Evidence Report/Technology Assessment

Number 212

Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer

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Number 212

Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer

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This report is based on research conducted by the Duke Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10066-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Disease Control and Prevention (CDC) requested and provided funding for this report.

The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the Evidence-based Practice Center (EPC) consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, the Evidence-based Practice Center (EPC) sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer

Structured Abstract

Objective. To estimate the overall balance of harms and benefits from the potential use of oral contraceptives (OCs) for the primary prevention of ovarian cancer

Data sources. We searched PubMed®, Embase®, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov for English-language studies published from January 1990 to June 2012 that evaluated the potential benefits (reduction in ovarian, colorectal, and endometrial cancers) and harms (increase in breast and cervical cancer, and vascular complications) of OC use.

Review methods. Two investigators screened each abstract and full-text article for inclusion; the investigators abstracted data, and they performed quality ratings, applicability ratings, and evidence grading. Random-effects models were used to compute summary estimates of effects. A simulation model was used to estimate the effects of OC use on the overall balance of benefits and harms.

Results. We reviewed 55 studies relevant to ovarian cancer outcomes, 66 relevant to other cancers, and 50 relevant to vascular events. Ovarian cancer incidence was significantly reduced in OC users (OR [odds ratio], 0.73; 95% CI [confidence interval], 0.66 to 0.81), with greater reductions seen with longer duration of use. Breast cancer incidence was slightly but significantly increased in OC users (OR, 1.08; 95% CI, 1.00 to 1.17), with a significant reduction in risk as time since last use increased. The risk of cervical cancer was significantly increased in women with persistent human papillomavirus infection who used OCs, but heterogeneity prevented a formal meta-analysis. Incidences of both colorectal cancer (OR, 0.86; 95% CI, 0.79 to 0.95) and endometrial cancer (OR, 0.57; 95% CI, 0.43 to 0.76) were significantly reduced by OC use. The risk of vascular events was increased in current OC users compared with nonusers, although the increase in myocardial infarction was not statistically significant. The overall strength of evidence for ovarian cancer prevention was moderate to low, primarily because of the lack of randomized trials and inconsistent reporting of important characteristics of use, such as duration. The simulation model predicted that the combined increase in risk of breast and cervical cancers and vascular events was likely to be equivalent to or greater than the decreased risk in ovarian cancer, although the harm/benefit ratio was much more favorable when protection against endometrial and colorectal cancers was added, resulting in net gains in life expectancy of approximately 1 month.

Conclusions. There is insufficient evidence to recommend for or against the use of OCs solely for the primary prevention of ovarian cancer. Although the net effects of the current patterns of OC use likely result in increased life expectancy when other noncontraceptive benefits are included, the harm/benefit ratio for ovarian cancer prevention alone is uncertain, particularly when the potential quality-of-life impact of breast cancer and vascular events are considered.

Contents

Tables

Figures

Appendixes

Executive Summary

Background

Ovarian cancer is the eighth most common cancer in women and is the fifth leading cause of cancer death, with an age-adjusted rate of 8.2 deaths per 100,000 women.[1] Given current age-specific incidence and demographic projections, the number of cases of ovarian cancer will almost double over the next 35 years as women born between 1946 and 1964 (the "baby boom" generation) reach the age of highest incidence (60 years and older).[2]

While advances in surgery, chemotherapy, and radiation therapy over the past 20 years have led to improved outcomes, overall 5-year survival is only 42 percent for ovarian cancer compared with 88 percent for breast cancer and 63 percent for colorectal cancer. The high mortality rate in women with ovarian cancer is largely attributed to the later stage at presentation compared with other common cancers. This has led to intense research efforts to identify effective screening strategies for ovarian cancer, but results have been disappointing, particularly with regard to decreases in mortality.

The lack of a detectible preinvasive lesion, as well as the lack of physical barriers to metastasis because of the ovary's location in the abdominal cavity, raise the possibility that effective screening strategies may not be possible outside of high-risk populations because the time from initial cancer development to metastasis may be too short to allow for feasible screening intervals. This possibility has been supported by mathematical modeling studies. The required high frequency of screening, combined with the relatively low incidence of ovarian cancer, would lead to high numbers of false positive results, even with a highly specific test. Given this, one reasonable alternative approach to reducing morbidity and mortality from ovarian cancer would be to identify effective primary prevention strategies.

Surgical prophylaxis through removal of the tubes and ovaries (bilateral salpingo-oophorectomy) has been used in women who are at a high risk of developing ovarian cancer due to the presence of a BRCA1 or BRCA2 mutation, and there are ongoing trials of its effectiveness compared with intense screening. However, given the morbidity associated with surgery, and the potential effects of early menopause, this is not considered a reasonable option for the general population. Similarly, although observational studies suggest that both hysterectomy with ovarian preservation and tubal sterilization reduce the risk of ovarian cancer, this potential benefit is not typically part of the decisionmaking process that leads a patient to undergo one of the procedures.

There is consistent evidence from a variety of sources that oral contraceptive (OC) use reduces ovarian cancer risk. This evidence includes declining age-specific ovarian cancer incidence and mortality in cohorts of women who had access to OCs throughout their reproductive life, and there are several biologically plausible mechanisms for a protective effect.

The potential benefit of using OCs solely to reduce the risk of ovarian cancer must be weighed with knowledge of other potential noncontraceptive health benefits of OCs and potential harms. No comparative effectiveness analyses have been conducted to inform decisions about the use of OCs as a primary preventive strategy for ovarian cancer. Also, because the majority of evidence on noncontraceptive benefits and harms of OC use is derived from observational studies (case control and cohort), careful consideration must be given to the potential biases inherent in those study designs when developing a research agenda and clinical recommendations, as evidenced by the experience with hormone replacement therapy for prevention of cardiovascular morbidity and mortality. The combination of systematic review and

decision-analytic modeling presented in this report allows us to estimate the tradeoff between the harms and benefits of OC use for the overall population and for individual women , accounting for the potential influence of other factors, such as timing of OC use or presence of risk factors such as family history.

Scope and Key Questions

This evidence report was funded by the Centers for Disease Control and Prevention (CDC) in conjunction with the Agency for Healthcare Research and Quality (AHRQ), and was designed to evaluate the benefits and harms of the use of oral contraceptives as a primary preventive measure against ovarian cancer. We focused on synthesizing the available evidence for the effectiveness of this strategy in a general population and in groups at elevated risk. We also evaluated benefits and harms of OC use that are not related to the development of ovarian cancer. Finally, we designed a comparative effectiveness model to inform the questions generated by this review.

The scope of the review specifically excluded the unquestioned effectiveness of OCs in preventing unintended pregnancies; the potential effectiveness of OCs as primary or adjunctive treatments for conditions such as menstrual disorders (e.g., dysmenorrhea or menorrhagia), endometriosis, or premenstrual dysphoric disorder; and the potential role of OCs in preventing the onset of these conditions.

Key Questions

With input from AHRQ, the CDC, and a Technical Expert Panel of external stakeholders, we defined Key Questions using the general approach of specifying the population of interest, interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS). The Key Questions (KQs) considered in this systematic review are:

KQ 1: What is the effectiveness of combined (estrogen and progestin containing) and progestin-only OCs for reducing the risk of ovarian cancer?

KQ 2: Do specifics of OC use (e.g., dose/formulation, age at initiation, duration of use) affect the relative risk of developing ovarian cancer?

KQ 3: Does the use of OCs by specific populations of women (e.g., those defined by age, family history of breast and ovarian cancer, BRCA1/BRCA2 mutation status, parity) affect the relative risk of developing ovarian cancer?

KQ 4: Aside from pregnancy prevention, are there other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

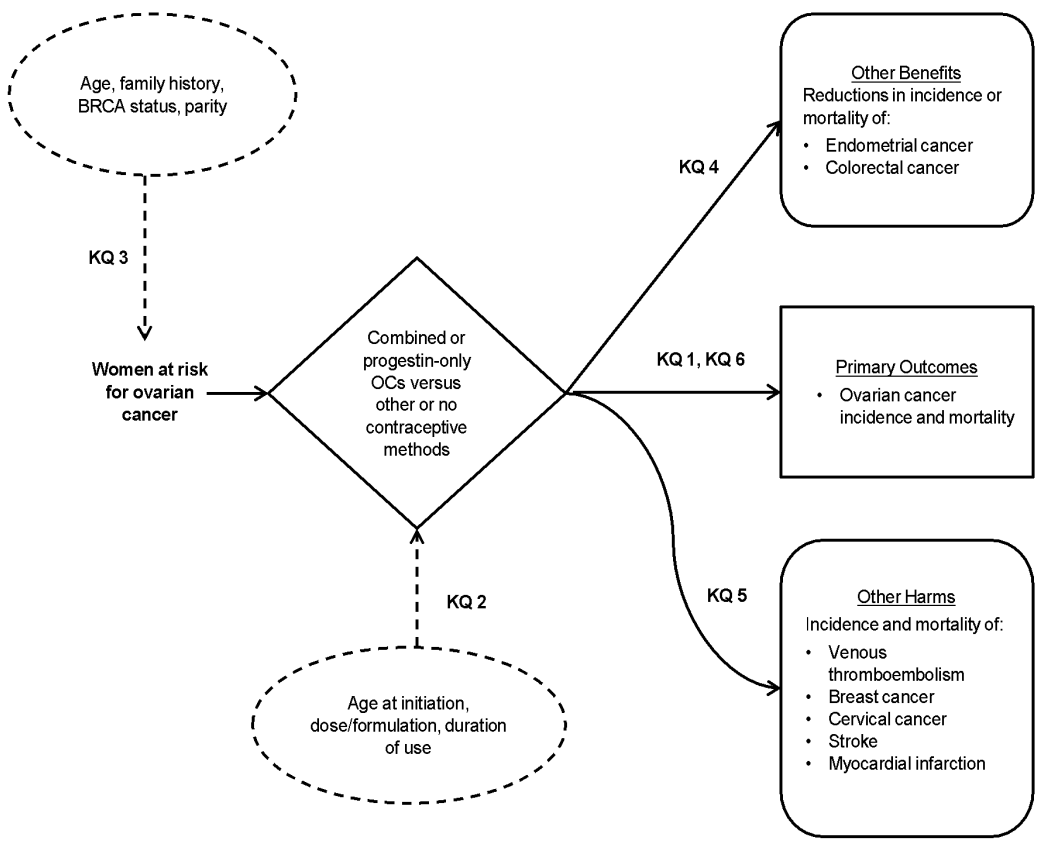
KQ 6: Based on the comprehensive literature review, what are the benefits and harms from the use of OCs to reduce the incidence of ovarian cancer for specific populations? Based on the decision model, what is the estimated effect of these benefits and harms on life expectancy and quality-adjusted life expectancy?

KQ 7: Based on the systematic review and decision model, what research gaps need to be filled to better understand whether OCs are effective for the primary prevention of ovarian cancer?

Analytic Framework

Figure A shows the analytic framework for this systematic review.

Figure A. Analytic framework for systematic review



BRCA = breast cancer genetic mutation; KQ = Key Question; OC = oral contraceptive
Note: KQ 7 is not shown in the analytic framework.

Organization of Report and Executive Summary

This report departs from the standard AHRQ evidence-report organization. The evidence is instead presented in four topic-focused sections. Three of the sections address the relationship between OC use and specific groups of benefits and/or harms: ovarian cancer (KQ 1, KQ 2, and KQ 3); breast, cervical, colorectal, and endometrial cancers (KQ 4 and KQ 5); and venous thromboembolism, stroke, and myocardial infarction (KQ 5). Within each section, the benefits and/or harms of OC use are considered for both the general population and specific populations of women for whom the risk levels of ovarian cancer are elevated. Each section also assesses

potential modifying factors such as dose, formulation, and duration of OC use, and considers specific evidence gaps and needs for future research regarding the association between OC use and the specific outcomes (KQ 7). The final section of the report uses a decision analytic framework to explore the overall benefits and harms from all outcomes considered in the report for both the general population and specific populations (KQ 6), as well as identifies additional evidence gaps and needs for future research related to the potential overall benefits and harms of OCs for the prevention of ovarian cancer (KQ 7). For the purposes of this Executive Summary, we present the results organized by Key Question.

Methods

The methods for this evidence report follow those suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews," hereafter referred to as "Methods Guide" (www.effectivehealthcare.ahrq.gov/methodsguide.cfm).[3]

Literature Search Strategy

We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews to identify relevant literature published from January 1990 to June 2012, using the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. We restricted the search to articles published subsequent to January 1990 to increase the likelihood that the types of OCs used by the women in the studies we retrieved were similar to those currently available, maximizing the generalizability and clinical relevance of the results. We also searched the ClinicalTrials.gov registry to identify additional relevant articles from completed studies.

We supplemented the electronic searches with a manual search of citations from a set of key review articles. The reference lists from these articles were hand-searched and cross-referenced against our library of database search results. Additional relevant articles not already under consideration were retrieved for screening. All citations were imported into an electronic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA). We did not systematically search gray literature databases beyond ClinicalTrials.gov, since the high volume of literature identified through our searches of peer-reviewed articles made it unlikely that further searching of gray literature would substantially increase the chances of identifying relevant data that would meet inclusion criteria. We invited drug manufacturers to submit additional information through a scientific information packets request, which was sent by AHRQ on our behalf. Submissions received through this mechanism were reviewed, and relevant citations were screened against the review inclusion/exclusion criteria.

Inclusion and Exclusion Criteria

Table A presents the inclusion/exclusion criteria for this systematic review.

Table A. Summary of inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• All KQs: ○ Women taking OCs for contraception or women taking OCs for primary prevention of ovarian cancer[a] ○ Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy • KQs 3 and 6: ○ Women with a family history of ovarian or premenopausal breast cancer, suggesting increased risk according to current recommendations ○ Women with a known BRCA1/BRCA2 mutation	Nonhuman studies
Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	Studies that do not provide a description of at least one of the following: (1) OC formulation(s) used (2) Length of OC use (Not required for studies reporting ovarian cancer outcomes or conducted in a population taking OCs for primary prevention of ovarian cancer)
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Studies that do not include controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable) Studies comparing OC formulations (without including a non-OC control) are acceptable for studies reporting venous thromboembolism, stroke, or MI outcomes
Outcomes	Study reports quantitative association between exposure to OCs and one of the outcomes listed below: • KQs 1, 2, 3, 6: ○ Diagnosis of ovarian cancer, ovarian cancer mortality ○ Adverse effects (see KQ 5) • KQ 4: ○ Diagnosis of endometrial cancer, endometrial cancer mortality, diagnosis of colorectal cancer, colorectal cancer mortality ○ Adverse effects (see KQ 5) • KQ 5: ○ Diagnosis of breast cancer, cervical cancer, venous thromboembolic event, stroke, or myocardial infarction; disease-specific mortality associated with these outcomes • KQ 7: Not applicable	Study only reports outcomes related to assisted reproductive technologies or abortion

Table A. Summary of inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Timing	Studies of any duration	None
Setting	All settings	None
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor) • Exploratory study with inadequate sample size
Publications	• English-language only • Peer-reviewed articles • Outcome reporting falls within the following publication ranges: ○ Study reports an ovarian cancer outcome of interest and was published on or after Jan. 1,1990[d] ○ Study reports a breast, endometrial, cervical, or colorectal cancer outcome of interest and was published on or after Jan. 1, 2000[e] ○ Study reports a venous thromboembolic event, stroke, or myocardial infarction outcome of interest and was published on or after Jan. 1, 1995[f]	Non-English articles[g]

BRCA = breast cancer (genetic mutation); KQ = Key Question; OC = oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be for contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from direct abstraction, while those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies less than 100 subjects were excluded because confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]We considered studies published from January 2000 to June 2012 for the primary, ovarian cancer, outcome analyses. Older data (with publication dates beginning January 1990) were used to conduct sensitivity analyses, allowing us to compare the results from the January 2000 to June 2012 analyses with those from a longer date range (January 1990 to June 2012).

[e]Date ranges for these cancer outcomes were selected to balance generalizability (OC formulations used in earlier studies not currently on market) and power (peak incidence of cancers 10 to 30 years after typical use of oral contraceptives).

[f]Date ranges for acute vascular events associated with OC use were restricted to more recent years to reflect currently available formulations.

[g]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies), and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Study Selection

Using the inclusion and exclusion criteria described in Table A, two investigators independently reviewed the titles and abstracts of articles retrieved through the search strategies for potential relevance to the KQs. Articles included by either reviewer were promoted to full-text screening. At the full-text screening stage, two investigators independently reviewed the full text of each article and indicated a decision to include or exclude the article for data abstraction. When paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, we reconciled the difference through review and discussion among investigators. Articles meeting eligibility criteria were included for data abstraction. All screening decisions were made and tracked in a DistillerSR database (Evidence Partners, Manotick, ON, Canada).

Data Extraction

The investigative team created forms for abstracting the data elements for the KQs, which were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors for accuracy. A pair of researchers with complementary clinical and methodological expertise was assigned to abstract data from the eligible articles. One researcher abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third researcher's opinion if consensus could not be reached by the first two researchers.

To aid in both reproducibility and standardization of data collection, guidance documents were drafted and given to the researchers as reference material. The forms for the researchers, created via the DistillerSR data synthesis software, contained further data abstraction instructions. We designed the data abstraction forms to collect information required to conduct the review, which included the following: data needed to evaluate the specified eligibility criteria for inclusion; demographic and other relevant patient characteristics (e.g., family history of ovarian cancer); details of the interventions and comparators (e.g., OC dose, formulation, patterns of use); outcome measures and adjustment factors applied in study analyses; and data needed to assess quality and applicability.

Risk-of-Bias Assessment of Individual Studies

The included studies were assessed using the approach described in AHRQ's "Methods Guide."[3] To assess quality, we used the approach to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. To evaluate methodological quality, we applied criteria for each study type derived from core elements described in the "Methods Guide." Criteria of interest for all studies included similarity of groups at baseline, the extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. No randomized controlled trials were identified for inclusion in this review; thus, criteria specific to randomized studies (e.g., methods of randomization and allocation concealment) were not considered.

Additional elements considered for observational studies included methods for selection of participants and management of selection bias, measurement of interventions/exposures, addressing any design-specific issues, and controlling confounding. To indicate the summary judgment of the quality for the individual studies, we used the summary ratings of good, fair, and poor. For each study, one investigator assigned a summary-quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached. In some cases, data from a study composed of more than one article could not be combined into one abstraction. In those instances, the quality ratings for individual abstractions within a study grouping could vary based on the specific component articles' quality of reporting, the evaluated outcomes, and the statistical and analytical methods used.

Data Synthesis

After data extraction, we determined the feasibility of completing a quantitative synthesis by assessing the volume of relevant literature, the conceptual homogeneity of studies, and the completeness of results reporting. Outcomes assessed by meta-analysis, if feasible, included disease-specific incidence, disease-specific mortality, and disease-specific survival. Our general approach for each outcome was to analyze, if possible, the following associations: (1) temporal relationships (current vs. noncurrent OC use, ever vs. never OC use, and duration of current OC use), (2) OC formulation (estrogen dose [high vs. low], progestin generation [first, second, third, and fourth generations]), and (3) special populations (such as women with known family history or genetic predisposition).

When study designs and outcomes reported were similar and the population in the study was broad (e.g., not factor V Leiden carriers), we estimated pooled odds ratios with 95% confidence intervals (95% confidence intervals [CIs]) using a random-effects model. We evaluated heterogeneity visually and with the Cochran Q statistic using a threshold p-value of less than 0.10. We stratified analyses by study type (i.e., case-control, cohort, pooled analyses). All meta-analyses were performed using Comprehensive Meta-Analysis Version 2.0.[4]

Results were discussed qualitatively when study numbers were insufficient for meta-analysis (less than three), when confidence intervals around measures of association were not reported or could not be calculated, or when a study included a special population that was not likely to be representative of the general population of women aged 15 to 44.

We included data from pooled analysis articles in our meta-analysis if (1) none of the individual studies included in the pooled analysis had already been included for meta-analysis, (2) at least half the studies in the pooled analysis were published on or after the date threshold applied for the outcome under consideration in the analysis, and (3) data in the pooled analysis were presented such that inclusion in the current meta-analysis was feasible.

For the outcomes of cumulative lifetime incidence and mortality, life expectancy, numbers needed to harm and prevent, and harm-to-benefit ratios, we constructed a semi-Markov state-transition model of a cohort of women aged 10 to 100, using TreeAge Pro 2012 (TreeAge Software, Inc., Williamstown, MA). Relative risk estimates were derived from the meta-analyses and other age-specific and race-specific probabilities that were obtained from the literature or publicly-available data sources. The model was run as a microsimulation, which allowed for conditioning of probabilities based on past history. Depending on the analysis, each model run included 5,000 to 1,000,000 simulated individuals; estimates of the outcomes of interest were based on the mean value of each model run (or, in some cases, the weighted average of multiple model runs).

Estimates were derived for both the overall population, given current OC use patterns (i.e., the cumulative effect of current patterns of age of starting OCs, as well as duration of use, on the outcomes of interest [based on the risk estimates] compared with a scenario where OCs had no effect on risk), as well as on an individual level (the cumulative effect of OC use in all users, based on current patterns of use, vs. nonusers). The impact of varying age of starting OC use and duration of use was assessed in a separate analysis.

Finally, we assessed the impact of uncertainty in the estimates of OC effects by using a method analogous to cost-effectiveness analysis. Instead of estimating a cost-effectiveness ratio, we estimated harm-to-benefit ratios, where total harms were considered “costs,” and total benefits “effectiveness.” We assessed the impact of uncertainty in the effects of OC use on both harms and benefits (based on the confidence intervals of the relative risk estimate) and on

whether OC use would be recommended based on different "willingness-to-pay" thresholds according to the harm-to-benefit ratio.

Strength of the Body of Evidence

The strength of evidence for each Key Question and outcome was assessed using the approach described in the "Methods Guide."[3,5] The evidence was evaluated using the four required domains of (1) risk of bias, (2) consistency, (3) directness, and (4) precision. Additionally, when appropriate, the studies were evaluated for dose-response association, the presence of confounders that diminished an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of "high," "moderate," or "low" for strength of evidence was assigned by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make (for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit a conclusion to be drawn). In these situations, a grade of "insufficient" was assigned.

Applicability

To assess applicability, we used the PICOTS format to identify specific issues that could limit the applicability of individual studies or a body of evidence, as recommended in the "Methods Guide."[3,6] We used data abstracted on the populations studied, the interventions and comparators, the outcomes measured, study settings, and timing of assessments to identify specific issues that could limit the applicability of individual studies or a body of evidence.

Specific factors affecting applicability included (but were not limited to): (1) population, including indication for use (we anticipated that most of the literature would be based on women using OCs for contraception, not for primary prevention of ovarian cancer), and the distribution of risk factors, such as genetic predisposition, age, reproductive history, and smoking, that might affect the relative likelihood of different harms and benefits; (2) intervention and comparator, particularly the OC formulation since the lag time between exposure and onset of cancer means that the OCs used by women in observational studies may differ from currently available OCs; and (3) outcomes, since data on all relevant outcomes, particularly cancers, may not be available for newer OCs.

We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use, and clinical relevance and timing of the outcome measures.

Results

The main results of the review are presented in this Executive Summary organized by KQ; more detailed descriptions are provided in the full report.

Literature Search Results

Searches of PubMed, Embase, and the Cochrane Database of Systematic Reviews yielded 7,196 citations, 767 of which were duplicates. Manual searching and contacts with drug manufacturers via the scientific information packet requests identified 47 additional citations, for a total of 6,476. No additional relevant citations beyond those already identified were found

during a search of relevant studies listed on ClinicalTrials.gov. After applying inclusion and exclusion criteria at the title-and-abstract level, 1,919 full-text articles were retrieved and screened. Of those, 1,671 were excluded at the full-text screening stage, leaving 248 articles (representing 157 unique studies) for data abstraction. As indicated in Figure 8 in the full report, several articles and studies were relevant to more than one outcome of interest—55 relevant to ovarian cancer outcomes (KQ 1, KQ 2, KQ 3), 66 to other cancers of interest (KQ 4, KQ 5), and 50 to vascular events (KQ 5).

Key Question 1. Effectiveness of OC Use for Reducing Incidence of Ovarian Cancer

Table B shows the strength of evidence for the effect of OC use on ovarian cancer. We identified 55 studies that evaluated the association between OC use and the incidence of ovarian cancer. Of these, 39 were case-control studies, 10 were cohort studies, and 6 were pooled analyses. None of the pooled analyses met criteria for inclusion in the meta-analyses examining OC use and ovarian cancer incidence. (Criteria for inclusion of studies in the meta-analyses, and reasons for excluding any studies that were not incorporated, are described in the full report.) Ever use of OCs was consistently associated with a decreased risk of developing invasive ovarian cancer (odds ratio [OR], 0.73; 95% CI, 0.66 to 0.81). Ever use of OCs was significantly associated with a decreased risk of dying from invasive ovarian cancer in two large cohort studies, although formal meta-analysis was not performed. Although results were consistent, direct, and precise for ever use versus never use and for duration of use, strength of evidence was moderate because of the persistent risk of bias due to the observational nature of the studies.

Table B. Strength of evidence domains for the effect of OC use on ovarian cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ovarian Cancer in Overall Population						
Ever vs. never use	24 (657,055 women and 3,981,072 person-years)	Medium	Consistent	Direct	Precise	**Moderate** 0.73 (0.66 to 0.81)
Duration of use	15 (547,363 women and 3,493,072 person-years)	Medium	Consistent	Direct	Precise	**Moderate** 1–12 mo: 0.91 (0.78 to 1.07) 13–60 mo: 0.77 (0.66 to 0.89) 61–120 mo: 0.65 (0.55 to 0.77) >120 mo: 0.43 (0.37 to 0.51)
Age at first use	6 (111,817 women)	High	Consistent	Direct	Imprecise	**Low** <20 yr: 0.63 (0.45 to 0.89) 20–24 yr: 0.71 (0.51 to 0.99) 25–30 yr: 0.67 (0.46 to 0.99) > 30 yr: 0.89 (0.60 to 1.32)

Table B. Strength of evidence domains for the effect of OC use on ovarian cancer (continued)

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ovarian Cancer in Overall Population (continued)						
Time since last use	8 (210,069 women and 1,083,000 person-years)	High	Inconsistent	Direct	Imprecise	**Low** 0–10 yr: 0.41 (0.34 to 0.50) 10–20 yr: 0.65 (0.56 to 0.74) 20–30 yr: 0.92 (0.76 to 1.12) >30 yr: 0.79 (0.58 to 1.12)
High-dose vs. low-dose estrogen	6 (9,007 women)	High	Consistent	Indirect	Imprecise	**Low** 1.25 (0.95 to 1.64)
High-dose vs. low-dose progestin	4 (7,528 women)	High	Inconsistent	Indirect	Imprecise	**Low** 0.86 (0.60 to 1.21)
Incidence in BRCA1- or BRCA2-Positive Women						
Ever vs. never use	3 (6,855 women)	Medium	Consistent	Direct	Precise	**Moderate** 0.58 (0.46 to 0.73)
Incidence in BRCA1-Positive Women						
Ever vs. never use	4 (5,519 women)	Medium	Consistent	Direct	Precise	**Moderate** 0.55 (0.47 to 0.66)
Incidence in BRCA2-Positive Women						
Ever vs. never use	3 (1,592 women)	Medium	Inconsistent	Direct	Imprecise	**Low** 0.65 (0.34 to 1.24)
Incidence in Women With Family History						
Ever vs. never use	3 (9,193 women)	High	Inconsistent	Direct	Imprecise	**Low** Decreased incidence
Incidence in Gravid/Parous and NulligravidNulliparous Women						
Ever vs. never use	2 (4,732 women)	Medium	Inconsistent	Direct	Imprecise	**Insufficient**
Mortality From Ovarian Cancer						
Ever vs. never use	2 (46,112 women and 602,700 person-years)	Medium	Consistent	Direct	Imprecise	**Moderate** Decreased cause-specific mortality
Survival Among Women With Ovarian Cancer						
Ever vs. never use	1 (676 women)	High	NA	Direct	Imprecise	**Insufficient** (not performed)[a]

BRCA = breast cancer genetic mutation; CI = confidence interval; mo = month/months; NA = not applicable; SOE = strength of evidence; yr = year/years

[a]The available data were not sufficient to perform a meta-analysis; refer to full report for details.

Key Question 2. Effect of Specifics of OC Use on Ovarian Cancer Incidence

Longer duration of OC use is significantly associated with greater reductions in ovarian cancer incidence (Table B). This conclusion is based on a meta-analysis of 15 studies. Of these,

10 were case-control studies representing 6,901 cases and 15,999 controls, and 5 were cohort studies representing 524,463 participants in 3 of the studies and 3,493,072 person-years in the other two studies. Seven studies were rated good quality, seven fair quality, and one poor quality. We excluded study datasets that reported fewer than three duration categories; reported odds ratios only for specific subpopulations of women; lacked a "never use" reference group; reported duration data from the same trial as another included study; or reported duration odds ratios for only the year of OC use.

Earlier age at first OC use was associated with a nonsignificant trend toward a greater reduction in ovarian cancer incidence, but most studies did not adjust for potential confounding due to duration of use. This conclusion is based on a meta-analysis of six studies. Of these, 5 were case-control studies representing 3,552 cases and 4,713 controls, and 1 was a cohort study representing 103,552 participants. Four studies were rated good quality and two were rated fair quality. We excluded studies that reported on fewer than three age categories and studies that provided odds ratios for subpopulations only.

Time since last use was significantly associated with ovarian cancer incidence, based on a meta-analysis of eight studies. Of these, 5 were case-control studies representing 3,606 cases and 7,759 controls, and 3 were cohort studies representing 198,704 participants and 1,083,000 person years. Four studies were rated good quality and four were rated fair quality. We excluded studies that used fewer than three comparisons and studies that presented categories that were not amenable to a combined analysis. There was substantial heterogeneity among studies.

Separate meta-analyses of 6 studies of estrogen formulation (all case-control studies representing 2,607 cases and 6,400 controls, with 5 studies rated good quality and 1 rated fair quality, and with 1 exclusion because of insufficient dose information) and 4 studies of progestin formulation (all case-control studies, representing 2,049 cases and 5,479 controls, and all of good quality, with 3 exclusions because of incompatible progestin-dosing categorization) did not show any significant effect of steroid potency on the association between OC use and ovarian cancer; risk reductions were similar for high potency estrogen, low potency estrogen, high potency progestin, and low potency progestin.

Key Question 3. Relative Risk of Ovarian Cancer in OC Users in Subpopulations

Separate meta-analyses were performed for the following (Table B):

- BRCA1 and BRCA2 carriers (4 studies [1 good quality and 1 fair quality]: 3 were case-control studies with 1,096 cases and 2,878 controls, and 1 was a cohort study with 3,181 participants)
- Women of different gravidity and parity (2 case-control studies [both good quality] with 1,595 cases and 3,137 controls; 1 study was excluded because of data included in another paper)

Both analyses showed similar reductions in ovarian cancer risk with OC use independent of BRCA carrier status or gravidity/parity. Three case-control studies, one of good quality and two of fair quality, were identified that examined the effect of family history on the association between OC use and ovarian cancer. These studies were too heterogeneous in their description of subgroups for meaningful meta-analysis but, qualitatively, all showed similar reduction in ovarian cancer risk with OC use.

Key Question 4. Other Benefits of OC Use

Colorectal Cancer

Table C shows the strength of evidence for the effect of OC use on colorectal cancer. A pooled meta-analysis of 11 studies (3 case-control, 1 pooled analysis, and 7 cohort, of which 4 were good quality, 6 fair, and 1 poor) showed a significant reduction in the risk of colorectal cancer among ever users compared with never users (OR, 0.86; 95% CI, 0.79 to 0.95). There was no significant effect of duration of use. The two large United Kingdom (U.K.) cohort studies had conflicting results for colorectal cancer mortality in women with a history of OC use. As with ovarian cancer, the overall strength of evidence is reduced because of the risk of bias in observational studies.

Table C. Strength of evidence domains for the effect of OC use on colorectal cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Colorectal Cancer in Overall Population						
Ever vs. never use	11 (503,816 women across 8 studies and 2,969,189 person-years across 3 studies)	Medium	Consistent	Direct	Precise	**Moderate** 0.86 (0.79 to 0.95)
Duration of use	10 (167,555 women across 7 studies and 2,969,189 person-years across 3 studies)	Medium	Consistent	Direct	Imprecise	**Low** No increase in protective effect with prolonged use
Mortality From Colorectal Cancer						
Ever vs. never use	2 (46,112 women in 1 study and 602,700 person-years in a second study)	Medium	Inconsistent	Direct	Imprecise	**Insufficient** Mixed results for risk of death with ever use, and no trend toward increased protective effect with longer duration of use

CI = confidence interval; SOE = strength of evidence

Endometrial Cancer

Table D shows the strength of evidence for the effect of OC use on endometrial cancer. Seven studies (three case-control studies and four cohort studies: four good quality, two fair quality, and one poor quality) met inclusion/exclusion criteria for a meta-analysis of the association between OC use and endometrial cancer incidence; two studies were excluded for not reporting point estimates for ever versus never use. OC use significantly reduced the incidence of endometrial cancer (OR, 0.57; 95% CI, 0.43 to 0.76).

In a separate meta-analysis including eight studies (three case-control studies and five cohort studies: five good quality, two fair quality, and one poor quality), there was a significant trend toward a greater reduction in risk with increased duration of use. Two large U.K. cohort studies

showed a significant reduction in endometrial cancer mortality in women with a history of OC use. As with ovarian cancer, the overall strength of evidence is reduced because of the risk of bias in the observational studies.

Table D. Strength of evidence domains for the effect of OC use on endometrial cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Endometrial Cancer in Overall Population						
Ever vs. never use	7 (308,198 women across 4 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Precise	**Moderate** 0.57 (0.43 to 0.76)
Duration of use	8 (352,915 women across 5 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Imprecise	**Low** <60 months:0.78 (0.54 to 1.15) >60 months: 0.44 (0.29 to 0.65)
Mortality						
Ever vs. never use	2 (46,112 women in 1 study and 602,700 person-years in 1 study)	Medium	Consistent	Direct	Precise	**Moderate** Overall protective effect for ever use, which is greater for longer durations of use

CI = confidence interval; SOE = strength of evidence

Key Question 5. Harms of OC Use

Breast Cancer

Table E shows the strength of evidence for the effect of OC use on breast cancer. Ever use of OCs is associated with a small but significant increase in breast cancer risk, based on a combined meta-analysis of 15 case-control studies (9 good quality, 5 fair quality, and 1 poor quality) and 8 cohort studies (3 good quality, 4 fair, and 1 poor), with an odds ratio of 1.08 (95% CI, 1.00 to 1.17). Despite the increased incidence, there was no evidence of increased mortality from breast cancer (OR, 0.94; 95% CI, 0.87 to 1.02). We did not identify a relationship between duration of use and breast cancer risk, but risk significantly decreased with time since last use. The magnitude of the association between OC use and breast cancer was similar in BRCA1 and BRCA2 carriers, although confidence intervals included 1. The overall strength of evidence is reduced because of the risk of bias in observational studies.

Table E. Strength of evidence domains for the effect of OC use on breast cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Breast Cancer in Overall Population						
Ever vs. never use	23 (356,023 women across 20 studies and 3,981,072 person-years across 3 studies)	Medium	Consistent	Direct	Precise	**Moderate** 1.08 (1.00 to 1.17)
Duration of use	14 (291,407 women across 12 studies and 2,898,072 person-years across 2 studies)	Medium	Inconsistent	Direct	Imprecise	**Low** No increase in risk for longer durations of use
Time since last use	11 (200,258 women)	High	Inconsistent	Direct	Imprecise	**Low** Reduced risk over time since last use 0–5 yr: 1.21 (1.04 to 1.41) 5–10 yr: 1.17 (0.98 to 1.38) 10–20 yr: 1.13 (0.97 to 1.31) >20 yr: 1.02 (0.88 to 1.18)
Incidence in BRCA1- or BRCA2-Positive Women						
Ever vs. never use	5 (4,555 women across 4 studies and 65,180 person-years in 1 study)	Medium	Inconsistent	Direct	Imprecise	**Low** Trend toward slight increase in risk 1.21 (0.93 to 1.58)
Incidence in Women With Family History						
Ever vs. never use	3 (9,280 women)	High	Inconsistent	Direct	Imprecise	**Insufficient** Not performed
Incidence in Young Women						
Ever vs. never use	3 (5,716 women)	Medium	Inconsistent	Direct	Imprecise	**Insufficient** Not performed
Mortality From Breast Cancer						
Ever vs. never use	3 (54,606 women across 2 studies and 602,700 person-years in 1 study)	Medium	Consistent	Direct	Imprecise	**Low** No significant increase in risk 0.94 (0.87 to 1.02)
Survival After Diagnosis of Breast Cancer						
Ever vs. never use	3 (9,606 women)	Medium	Consistent	Direct	Imprecise	**Low** No significant increase in risk

BRCA = breast cancer genetic mutation; CI = confidence interval; SOE = strength of evidence; yr = year/years

Cervical Cancer

Table F shows the strength of evidence for the effect of OC use on cervical cancer. One fair-quality pooled analysis of eight separate case-control studies and two, poor quality, individual

case-control studies showed significant associations between OC use and an increased risk of invasive cervical cancer among women who were positive for human papillomavirus (HPV); risk was significantly associated with duration of use. Differences between studies precluded meta-analysis.

Because persistent HPV infection is a cause of cervical cancer, and because OC users may have other factors that put them at a higher risk of acquiring HPV, restricting analysis of the association between OCs and cervical cancer to HPV-positive women may be most informative. However, as a complement, we also performed a meta-analysis of nine studies that found a nonsignificant increase in cervical cancer risk among ever users (OR, 1.21; 95% CI, 0.91 to 1.61). Six studies (five case-control studies and one cohort study: three good quality and three fair quality) showed a nonsignificant increase in cervical cancer incidence with increasing duration of use (OR, 1.47; 95% CI, 0.91 to 2.38 for more than 60 months compared with never users).

Two large, fair-quality cohort studies conducted in the U.K. found an increased risk of cervical cancer mortality among OC users, with a trend toward increased mortality with a longer duration of use. The overall strength of evidence for the cervical cancer outcomes is reduced because of the risk of bias in observational studies.

Table F. Strength of evidence domains for the effect of OC use on cervical cancer

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Cervical Cancer in HPV-Positive Population						
Ever vs. never use	3 (2,592 women)	High	Inconsistent	Direct	Imprecise	**Insufficient** Unable to draw summary conclusion
Mortality from Cervical Cancer						
Ever vs. never use	2 (46,112 women in 1 study and 602,700 person-years in 1 study)	High	Consistent	Direct	Imprecise	**Low** Increased risk with ever use and longer duration of use

CI = confidence interval; HPV = human papillomavirus; SOE = strength of evidence

Venous Thromboembolism

Table G shows the strength of evidence for the effect of OC use on venous thromboembolic events. Based on a meta-analysis of 14 studies (6 good quality, 6 fair quality, 2 poor quality), current users of OCs have a three-fold increased risk of venous thromboembolism (OR, 2.97; 95% CI, 2.46 to 3.59). This elevated risk appears to be associated only with current use; we were unable to perform a meta-analysis because of the high degree of heterogeneity between studies. There was some evidence that risk of thromboembolism decreased with an increased duration of use, but there were not enough studies for a meta-analysis.

Although most studies included pulmonary embolism as one of several potential venous thromboembolic events, several studies that examined pulmonary embolism alone also found consistent increases in risk; however, the risk was somewhat smaller than for combined thromboembolism.

Results of a meta-analysis of three studies yielded inconclusive evidence regarding risk of venous thromboembolism (VTE) by estrogen dose. Another meta-analysis of six studies suggested a not statistically significant trend toward increased risk of VTE associated with third- and fourth-generation progestins. Results of a qualitative analysis of additional studies that directly compared progestin generations suggested that the risk of VTE is highest for third-generation progestins compared with levonorgestrel, a second-generation progestin. Although there were too few studies of progestin-only pills to perform meta-analysis, the studies that were identified showed no increase in risk in users of progestin-only pills compared with nonusers. The overall strength of evidence is reduced because of the risk of bias in observational studies.

Table G. Strength of evidence domains for the effect of OC use on venous thromboembolism

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of All VTE and Mixed DVT/PE						
Current vs. noncurrent use/never	14 (15,466 women plus 9,906,890 person-years)	Medium	Consistent	Direct	Precise	**High** 2.97 (2.46 to 3.59)
Incidence of PE Only						
Current vs. noncurrent use/never	3 (863 women plus 2,124,474 person-years)	Medium	Consistent	Direct	Precise	**Low** Elevated risk appears similar to that of VTE
Incidence of all VTE And Mixed DVT/PE						
Duration of use	5 (6,955 women plus 7,782,416 person-years)	Medium	Consistent	Direct	Precise	**Low** Elevated risk may be present during first year of use
Estrogen	3 (6,102 women plus 7,782,416 person-years)	Medium	Consistent	Direct	Precise	**High** Low dose: 3.39 (2.32 to 4.96) High dose: 3.06 (1.32 to 7.10)
Progestin	6 (16,048 women)	Medium	Consistent	Direct	Precise	**High** First generation: 4.06 (2.66 to 6.19) Second generation: 3.28 (2.49 to 4.31) Third generation: 4.06 (3.09 to 5.32) Fourth generation: 5.36 (2.78 to 10.32)
Mortality From VTE						
Current vs. noncurrent use/never	0	NA	NA	NA	NA	**Insufficient** NA

CI = confidence interval; DVT = deep venous thrombosis; NA = not available; PE = pulmonary embolism; SOE = strength of evidence; VTE = venous thromboembolism

Stroke

Table H shows the strength of evidence for the effect of OC use on stroke. In a meta-analysis of nine studies of ischemic or undifferentiated stroke, current OC users had a significant increase in risk compared with nonusers (OR, 2.15; 95% CI, 1.49 to 3.11). Results were similar when restricted to five case-control studies and two cohort studies of ischemic stroke (OR, 1.90; CI, 1.24 to 2.91), but not for four case-control studies of hemorrhagic stroke (OR, 1.03; CI, 0.71 to 1.49).

Past use or duration of use did not appear to be related to stroke risk, although we were unable to perform a meta-analysis. We were able to perform a meta-analysis of three case-control studies of estrogen level, which found a significant increase in risk with increased estrogen dose (although stroke risk with low-dose formulations was still significantly elevated compared with nonusers).

Evidence from three cohort studies did not show a significant increase in stroke-related mortality. The overall strength of evidence is reduced because of the risk of bias in observational studies.

Table H. Strength of evidence domains for the effect of OC use on stroke

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ischemic/Undifferentiated Stroke						
Current vs. noncurrent use/never	9 (54,767 women plus 310,564 person-years)	Medium	Consistent	Direct	Precise	**High** 2.15 (1.49 to 3.11)
Duration	4 (51,038 women plus 310,626 person-years)	Medium	Consistent	Direct	Imprecise	**Insufficient** NR (Insufficient evidence to support quantitative synthesis of findings)
Estrogen	3 (9,977 women)	Medium	Consistent	Direct	Precise	**High** Low dose: 1.73 (1.29 to 2.32) High dose: 4.10 (1.91 to 8.80)
Progestin	3 (6,994 women)	Medium	Inconsistent	Direct	Imprecise	**Insufficient** NR (heterogeneity in evidence about specific progestin generation)
Incidence of Ischemic Stroke						
Current vs. noncurrent use/never	7 (49,803 women plus 310,564 person-years)	Medium	Consistent	Direct	Precise	**High** 1.90 (1.24 to 2.91)

Table H. Strength of evidence domains for the effect of OC use on stroke (continued)

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Hemorrhagic Stroke						
Current vs. noncurrent use/never	4 (48,382 women)	Medium	Inconsistent	Direct	Imprecise	**Low** No difference, 1.03 (0.71 to 1.49)
Mortality From Stroke						
Current vs. noncurrent use/never	3 (46,112 women plus 3,091,673 person-years)	Medium	Consistent	Direct	Imprecise	**Moderate** 0.80 (0.59 to 1.08)

CI = confidence interval; NR = not reported; SOE = strength of evidence

Myocardial Infarction

Table I shows the strength of evidence for the effect of OC use on myocardial infarction (MI). A meta-analysis of eight studies (five case-control, two cohort, and one pooled case-control) found a nonsignificant increase in risk of MI among current users (OR, 1.34; 95% CI, 0.87 to 2.08). There were too few studies to perform a meta-analysis of duration of use or of estrogen dose. Risks were significantly higher with first-generation progestins compared with second- and third-generation formulations. The overall strength of evidence is reduced because of the risk of bias in observational studies.

Table I. Strength of evidence domains for the effect of OC use on myocardial infarction

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Myocardial Infarction						
Current vs. noncurrent use/never	8 (24,901 women plus 310,626 person-years)	Medium	Inconsistent	Direct	Imprecise	**Low** 1.34 (0.87 to 2.08)
Estrogen	2 (15,903 women)	Medium	Consistent	Direct	Imprecise	**Insufficient** NR
Progestin	5 (8,875 women)	Medium	Consistent	Direct	Precise	**High** First generation: 3.37 (2.04 to 5.54) Second generation: 1.79 (1.16 to 2.75) Third generation: 1.34 (0.91 to 1.98)

Table I. Strength of evidence domains for the effect of OC use on myocardial infarction (continued)

Comparison	Number of Studies (Women and/or Person-Years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Mortality From Myocardial Infarction						
Current vs. noncurrent use/never	3 (46,112 women plus 3,091,673 person-years)	Medium	Inconsistent	Direct	Imprecise	**Low** 0.85 (0.67 to 1.07)

CI = confidence interval; NR = not reported; SOE = strength of evidence

Key Question 6. Decision Analysis: Benefits and Harms of OC Use and Ovarian Cancer Risk

Using the point estimates from the ORs derived by the meta-analyses for each outcome (including those for MI and cervical cancer, which were not statistically significant), we estimated differences in age-specific incidence of cancers in OC ever users compared with never users (Figure B), and vascular events in current OC users versus noncurrent users (Figure C). Note that estimates are not adjusted for competing risks, such as hysterectomy or other-cause mortality, or for time-dependent factors, such as duration of use or time since last use.

Figure B. Increase or decrease in age-specific incidence of cancers in ever OC users versus never users

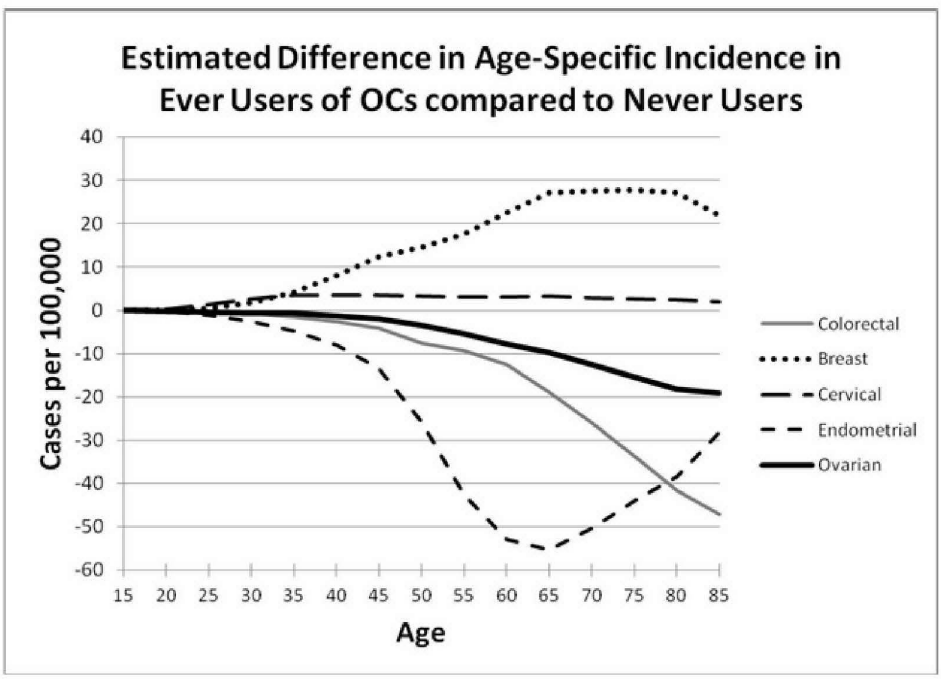
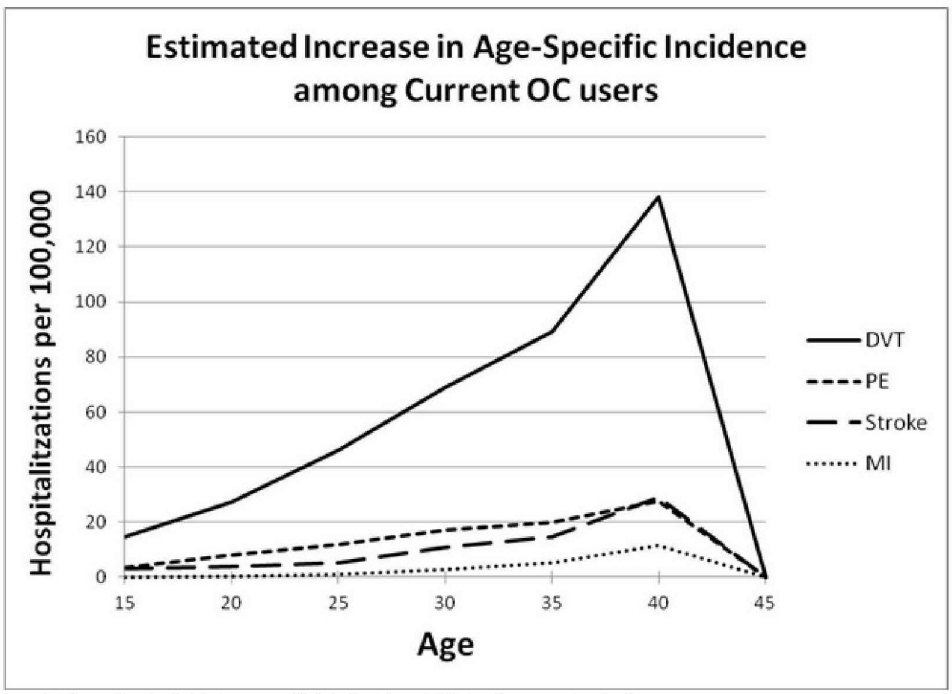


Figure C. Increase in age-specific incidence of vascular events in current OC users versus noncurrent users



DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism

We also developed a computer simulation model that integrated the findings of the meta-analyses with available data on population patterns of OC use, along with incidence and mortality data for cancers and vascular events, to estimate overall life expectancy and lifetime incidence and mortality for the general population given current patterns of OC use. We used two main types of comparisons. First, we performed a "counterfactual analysis," based on current population use, to estimate the population difference in outcomes if OCs were not associated with any of the harms or benefits considered in the review. The second analysis was a direct comparison to estimate the difference in outcomes between the average population of women who never used OCs and those who did.

At the population level, the model predicted decreases in incidence and mortality from ovarian, colorectal, and endometrial cancers, and increases in breast cancer incidence and mortality. Vascular events were increased in incidence. Mortality was increased to a lesser degree than incidence. For stroke, projected mortality incidence was decreased, likely due to a younger age distribution in OC users and subsequent higher post-event survival.

Using a model based on ever versus never use of OCs, mean life expectancy increased by approximately 1 month in users, a gain similar to that seen with other cancer prevention strategies in average-risk populations. An alternate version of the model that incorporated the effects of duration of OC use on ovarian cancer risk (increased duration associated with decreased risk), and time since last use on breast cancer risk (longer time associated with decreased risk) resulted in an estimated mean life expectancy gains of 2 months among users. When restricted to BRCA1 or BRCA2 carriers, the model predicted gains in women who used

OCs of almost 10 months in BRCA1 carriers (because of the much higher ovarian cancer risk) and 1 month in BRCA2 carriers.

For the second analysis (estimating the difference in outcomes between users and nonusers), the qualitative effects of OC use were similar to the population level analysis, but the magnitude was larger—estimated life expectancy gains of 10 months in the general population, 5 months in BRCA2 carriers, and over a year in BRCA1 carriers, for users compared with never users. Cause-specific mortality for some harms (particularly stroke) was reduced in OC users in this version of the model, which may be due to relatively small numbers of simulated subjects, the effect of different competing risks within the model structure, and/or the shift in age distribution.

Systematically varying age at first OC use and duration of use suggested that the harm-to-benefit ratio and life expectancy were optimized by 5 years' duration of use across all ages, with a relatively high harm-to-benefit ratio and decreased life expectancy with 10 years' duration of use for all but those who start OCs prior to age 20. Larger numbers of simulations are required to generate stable numbers given the low probability of many of these events, particularly in young women.

Using a net-benefits approach, we assessed the impact of different "willingness-to-pay" thresholds in terms of harms incurred versus benefits gained for both incidence and mortality, along with the relative contribution of specific clinical harms and benefits. The increase in breast cancer incidence was the greatest contributor to uncertainty regarding harms. For incident harms and benefits, the likelihood that benefits outweighed harms was less than 40 percent when only prevention of incident ovarian cancer was considered. Results were more favorable for mortality prevention, emphasizing the need for methods to incorporate quality of life, as well as mortality, into these analyses.

Key Question 7. Research Gaps

There were consistent evidence gaps across all of the literature we reviewed, and the modeling results suggested a few areas that should be prioritized. The greatest limitation to the existing literature is the potential for unmeasured confounding, which biases the estimates of the effects of OC use on these outcomes. Unfortunately, the size and duration of a randomized trial to definitively address the potential role of OCs as primary prevention for ovarian cancer would be unprecedented. Further work—using quantitative methods to estimate the potential benefit of primary prevention strategies for ovarian cancer, incorporating OCs—is needed to help clarify whether investing in such a large trial is worthwhile. There are few available data on patient preferences relevant to the use of OCs as primary prevention. Better data on the relative quality-of-life effects of regular OC use, and the outcomes we reviewed here, would allow for better assessment of the overall tradeoffs between harms and benefits at both the individual and population level.

There was inconsistent reporting of how variables, such as time since last use, duration of use, or OC formulation, were categorized. This was a major barrier to evidence synthesis, particularly since the model results showed that differences in assumptions about how these factors affect the association between OC use and outcomes can alter the overall balance of harms and benefits. Efforts to standardize reporting across studies should be strongly encouraged; study designs and analytic plans should be optimized to address these factors. Alternatively, pooled analyses of individual data collected across multiple studies offers an opportunity to address some of these shortcomings of reporting, but this approach is still

dependent on consistency in how data is collected. Given the feasibility issues of a randomized trial, this may be one of the only ways to better address confounding.

The overall impact on net harms and benefits of progestin-only pills, particularly for vascular events, is potentially better than for combination pills. Although this suggests progestin-only pills might be particularly well suited for primary prevention, there are fewer data available on cancer outcomes.

The effects of OC use on colorectal and breast cancer incidence were a major contributor to the overall balance of harms and benefits, and efforts to resolve remaining uncertainties regarding these two cancers should be prioritized.

Discussion

Key Findings and Strength of Evidence

The direction and size of the effect of OC use on the individual outcomes we assessed was consistent with previous systematic reviews. Previous modeling studies have suggested no net effect of OC use on life expectancy, while we estimated a gain of approximately 1 month. This difference likely reflects differences in the literature reviewed based on inclusion/exclusion criteria and the availability of more recent data, the inclusion of additional outcomes (particularly colorectal cancer), and the use of a stochastic microsimulation model to generate lifetime estimates in the face of competing risks.

The overall strength of evidence was moderate to low. There was general consistency across studies in both the direction and magnitude of the effect of OCs on disease incidence, but all of the empiric evidence was derived from observational studies, raising the possibility of unmeasured confounding. The results of the decision model do not contribute to the strength of evidence.

The noncontraceptive harms (increased risk of breast and cervical cancer and vascular events) and benefits (decreased risk of ovarian, colorectal, and endometrial cancers) associated with OC use can affect both quality of life and mortality. Based on the available evidence, the current patterns of combination OC use in the general population, likely result in a net increase in life expectancy of at least 1 to 2 months, which is comparable to many other preventive interventions. This is in addition to the beneficial effects of prevention of unwanted pregnancy. The likelihood that OC use decreases life expectancy is low, but there is insufficient evidence to estimate the overall effects on quality of life. It is important to note that there is substantially more evidence on the effects of OCs on the incidence of relevant outcomes than there is on mortality related to those outcomes, and estimates of their effect on mortality derived from a model are even more uncertain than estimates for incident events.

These results may be reassuring to women considering OCs for contraception and to women who are prescribed OCs for treatment of other conditions. There is substantial remaining uncertainty about the joint effects of age at first OC use and duration of use on optimizing the net noncontraceptive benefits of OCs. There is insufficient evidence to recommend OCs solely for the prevention of ovarian cancer for women who would not be considering OC use for another indication. For these women, the available evidence suggests that the increase in risk of developing breast cancer or having a vascular event is likely to be approximately the same as, or slightly greater than, the decrease in risk of developing ovarian cancer. Because deaths from those harms, even in the aggregate, are lower than for ovarian cancer, there may be benefits in terms of mortality. However, the quality-of-life impact of those harms, particularly stroke and

MI, may be substantial. The benefit-to-harm ratio for both incident benefits and harms, and mortality from those outcomes, from using OCs as a primary preventive agent is substantially improved when potential reductions in colorectal and endometrial cancers are included.

Applicability

Applicability of the evidence to current U.S. practice is limited by several factors. Most importantly, the long duration between exposure to OCs and development of cancers means that the available evidence is based on a different distribution of OC formulations than are currently on the market. This long lag time may also contribute to unmeasured cohort effects in factors such as smoking, parity, or hysterectomy rates, which alter the risk of the outcomes we considered in both OC users and nonusers.

Many of the largest and most complete studies were performed outside of the United States. Differences in formulations, in prevalence of genetic and acquired factors affecting outcome risk, and in health-system characteristics, such as population coverage for cancer screening, may affect study results.

Finally, OCs have been available only since the 1960s, meaning that birth cohorts of women with a high prevalence of OC use are only now entering the age of peak incidence for many cancers. Predictions of the long-term effects of OC use are necessarily based on population-based, age-specific incidence and mortality data. Because these data are cross-sectional, estimates for older women reflect cohorts that were relatively unexposed to OCs. If OC use does significantly affect the incidence of certain cancers, then predictions of the long-term impact of prescribing OCs today will be in error.

Conclusions

The available evidence suggests that incident harms associated with OC use are likely to exceed prevented cases of ovarian cancer. The overall net effect of current patterns of OC use on deaths from noncontraceptive outcomes is positive, with reductions in mortality from ovarian, colorectal, and endometrial cancers exceeding increased deaths from breast cancer and vascular events. There is uncertainty about the magnitude of this effect, but the probability of a negative impact on life expectancy is small and may be reassuring to women considering OCs as a contraceptive method. There is insufficient evidence to recommend for or against the use of OCs solely for the primary prevention of ovarian cancer.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BRCA	breast cancer genetic mutation
CDC	Centers for Disease Control and Prevention
CI	confidence interval
HPV	human papilloma virus
KQ	Key Question
MI	myocardial infarction
OC	oral contraceptive
OR	odds ratio
PICOTS	population, interventions, comparators, outcomes, timing, settings
VTE	venous thromboembolism

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Section 1. Introduction and Methods

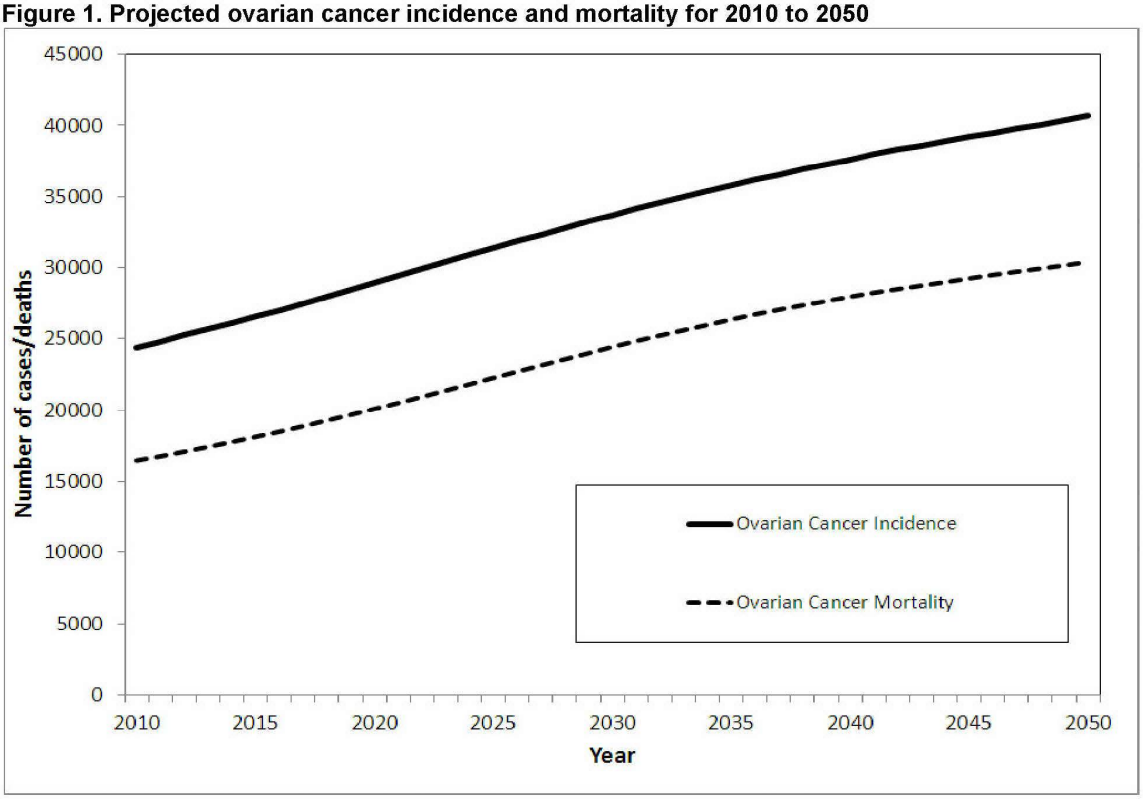
This evidence report was funded by the Centers for Disease Control and Prevention (CDC) in conjunction with the Agency for Healthcare Research and Quality (AHRQ) and was designed to evaluate the benefits and harms of the use of oral contraceptives as a primary preventive measure against ovarian cancer.

Background

Ovarian Cancer Incidence and Mortality

Although ovarian cancer is only the eighth most common cancer in women (annual age-adjusted incidence 12.3 per 100,000), it is the fifth leading cause of women's cancer deaths (8.2 per 100,000).[1] Given current age-specific incidence data and U.S. Census demographic projections, the estimated annual number of new ovarian cancer cases will almost double (to 40,000) over the next 35 years as women born between 1946 and 1964 (the "baby boom" generation) reach the ages of highest risk (Figure 1).[2]

Figure 1. Projected ovarian cancer incidence and mortality for 2010 to 2050

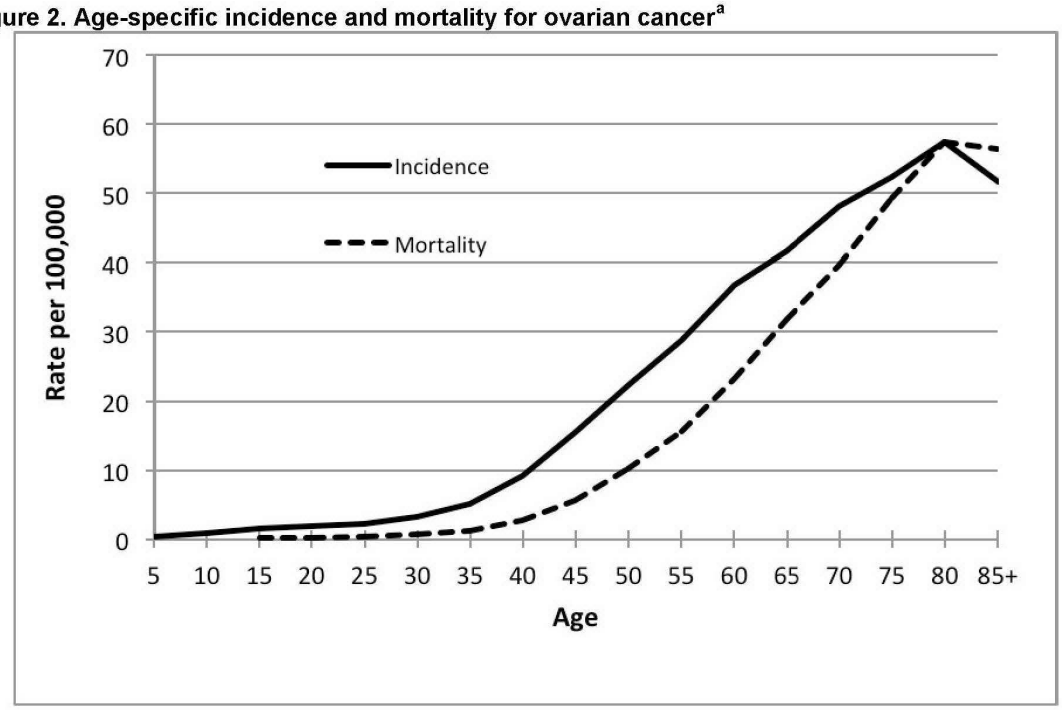


Trends

Age-Specific Incidence and Mortality

Age-specific ovarian cancer incidence and mortality follow a similar pattern that is consistent with the high case-to-fatality ratio of ovarian cancer (Figure 2).

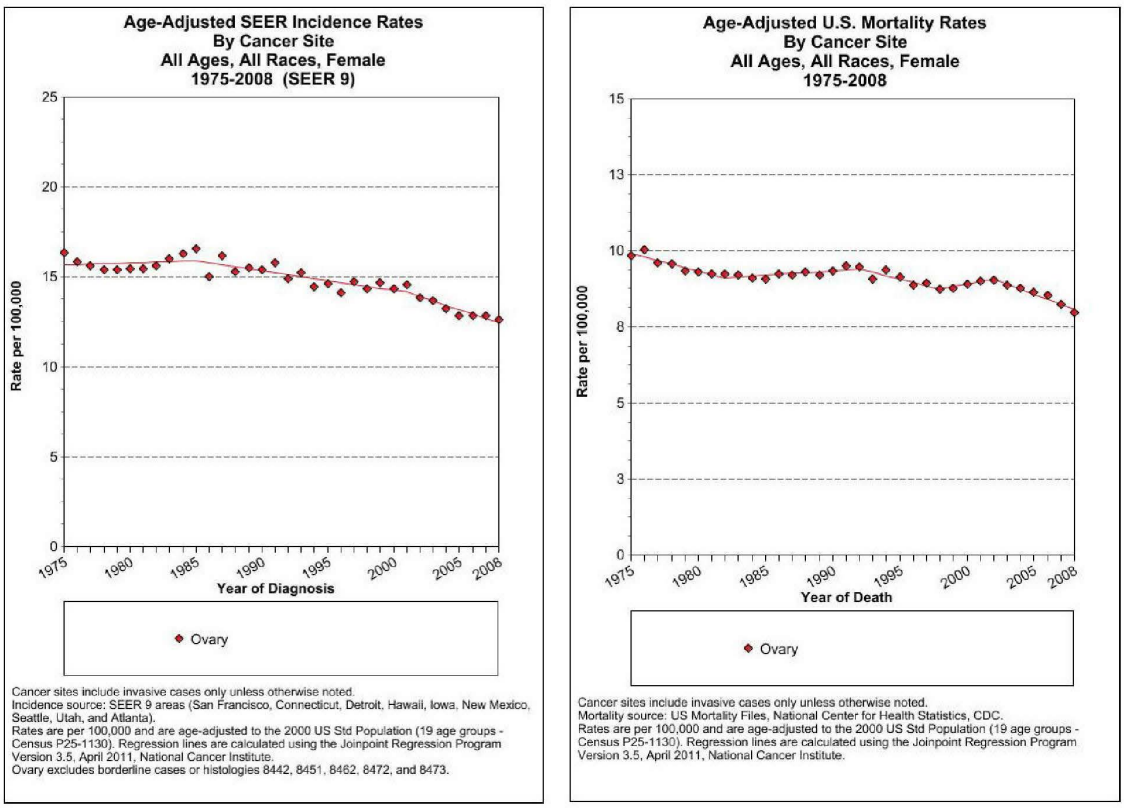
Figure 2. Age-specific incidence and mortality for ovarian cancer[a]



[a]Surveillance, Epidemiology, and End Results (SEER), 2000–2008.

After a slight decline from 1975 through 1985, age-adjusted ovarian cancer mortality was mostly stable until 2002, when mortality had dropped by an annual rate of 1.7 percent (Figure 3). At the same time, age-adjusted incidence was also declining.[3] There are three potential explanations for this decreased mortality: improved survival after diagnosis because of improved treatments, improved survival through effective screening, or decreased incidence. Some of this decrease in mortality may be attributed to the cumulative effects of recent advancements in the treatment of ovarian cancer, which include recognition of the importance of aggressive primary cytoreductive surgery, introduction of platinum- and taxane-based chemotherapy, and introduction of the intraperitoneal route of chemotherapy administration.

Figure 3. Age-adjusted ovarian cancer incidence and mortality rates



Lack of Effectiveness of Screening

Despite the advances in primary treatment, the mortality rate for ovarian cancer remains the highest among the gynecologic malignancies. Because ovarian cancer typically presents at a much later stage (with concomitant higher mortality) than other common cancers,[1] there has been intense interest in developing effective screening strategies.

Unfortunately, these efforts have had disappointing results to date, especially in the ability of screening to result in reduced mortality.[4-10] Several factors limit the success of screening for ovarian cancer. First, the cause and pathogenesis of the disease remain unknown. While certain histologic subtypes have been associated with precursor lesions, there is still no preinvasive "Stage 0" lesion that is universal, definitive, and detectible. Second, there is no physical barrier to impede rapid spread of malignant cells from the surface of the ovary (FIGO Stage I) (or, as a growing body of evidence suggests, from the epithelium of the fallopian tube) to the upper abdomen (FIGO Stage III).[11] The possibility of rapid spread from the ovary means that many of the cancers identified at Stage I may represent a subgroup of less aggressive tumors rather than a necessary first step in the development of all tumors. Recent pathogenetic studies support the heterogeneity of ovarian cancer, with some subtypes acting as more indolent lesions that are more likely to be detected in an early stage and to be more curable.[12] If this is the case, screening, which is more likely to identify slower growing tumors, may have only a limited impact on overall ovarian cancer mortality.[13] Recently, the Prostate, Lung, Colorectal, and

Ovarian Phase III ovarian cancer screening trial reported no clinical benefit—and noted possible harm due to false-positive results—when postmenopausal women were screened annually for up to 6 years with CA-125 and pelvic ultrasound.[10]

A second large Phase III trial, the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS),[7] randomized women to usual care, ultrasound-based screening, or a multimodality screening algorithm consisting of a CA-125 followed by ultrasound for those with abnormal or rising CA-125 results. The UKCTOCS trial has released the results of prevalence screening, with an encouraging shift toward detection at earlier disease stages noted. However, the mortality outcomes of this trial are not yet known and, as such, the benefit of screening for ovarian cancer remains unproven.

Primary Prevention

Given that the potential effectiveness of screening to reduce morbidity and mortality from ovarian cancer appears to be limited by the underlying biology of the disease, alternative strategies—including the use of more efficacious and less toxic therapies after diagnosis as well as primary prevention—need to be considered and evaluated.

Surgery

Surgical prophylaxis, in the form of bilateral salpingo-oophorectomy (BSO), is a primary preventive approach to ovarian cancer that has been widely used only for women at high genetic risk. In a BRCA1/2 mutation–carrying population, BSO has been demonstrated to reduce the risk of ovarian, tubal, or peritoneal cancers by 80 percent and the risk of breast cancers by 50 percent.[14] The Gynecologic Oncology Group is currently completing a nonrandomized prospective trial comparing risk-reducing salpingo-oophorectomy to longitudinal screening with CA-125 and ultrasound. Several groups have performed health-economic models suggesting that prophylactic surgery is both effective and cost-effective in the BRCA carrier population.[15,16] Given the potential harms of prophylactic surgery and premature loss of ovarian function, surgical prophylaxis in the absence of other indications for pelvic surgery has not been recommended in the general premenopausal population. There is also evidence from observational studies that two gynecological surgical procedures performed for other indications, tubal sterilization and hysterectomy,[17-19] also reduce ovarian cancer risk, even without removal of the ovaries. In light of accumulating evidence that many, if not most, ovarian cancers originate in the fallopian tube, some groups, notably the British Columbia Cancer Association, are advocating removal of the tubes at the time of surgical sterilization or hysterectomy for other indications, but there is no evidence on potential effectiveness.[20]

Oral Contraceptives

Oral contraceptives (OCs) represent a potentially promising primary prevention strategy for ovarian cancer. Several studies suggest a protective effect of OCs on ovarian cancer risk, with a reduction in risk of up to 50 percent with long-term use.[21,22]

Age-Period Cohort

Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry suggest a reduction in both age-specific incidence and mortality in cohorts born in 1940 or later (i.e., those who had access to OCs during their entire reproductive life span). Figure 4 shows age-specific incidence, and Figure 5 shows age-specific mortality by age-period

cohort, derived from SEER age-specific incidence and mortality data from 1974 to 2008. Lines refer to women born in the indicated year.

Figure 4. Age-specific incidence by age-period cohort

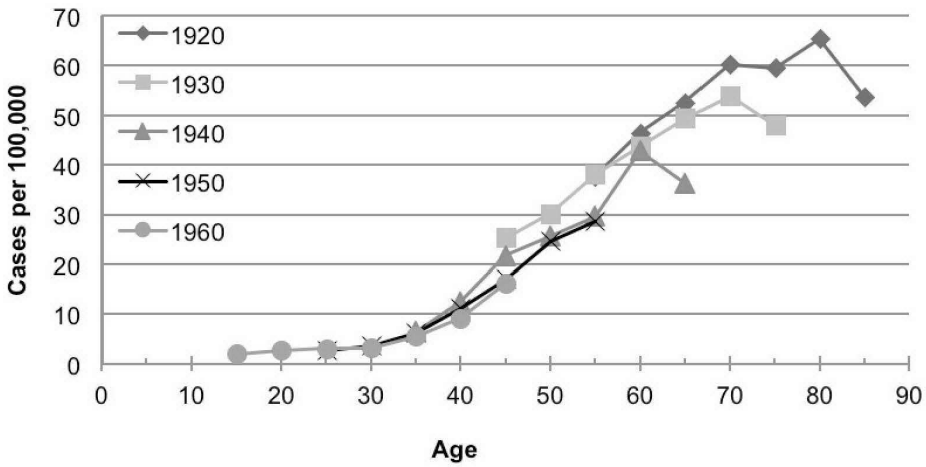
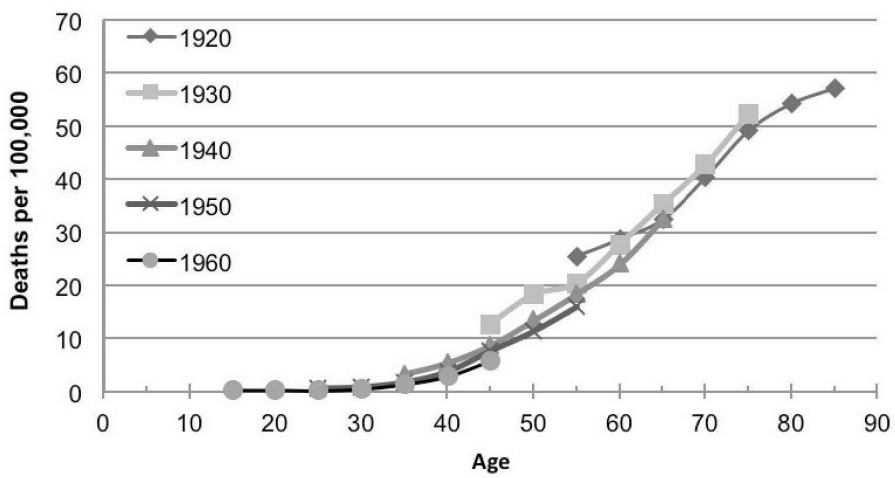


Figure 5. Age-specific mortality by age-period cohort



Clinical Data

A large number of observational studies provide evidence that OC use has a protective effect on ovarian cancer incidence and mortality. The largest pooled analysis combined data from 45 epidemiological studies in 21 countries representing 23,257 women with ovarian cancer and 87,303 controls. This analysis described an odds ratio for ever OC use of 0.73 (95% CI, 0.70 to 0.76). There was a strong relationship between degree of risk and duration of OC use, with the overall risk decreased by 20 percent (95% CI, 18% to 23%) for every 5 years of OC use. Based on these findings the authors estimated that use of OCs has already prevented 200,000 ovarian cancers and 100,000 deaths from ovarian cancer.[21] Two other pooled analyses of epithelial ovarian cancer had consistent findings, with odds ratios for ever OC use of 0.66 (95% CI, 0.56 to 0.79) and 0.6 (95% CI, 0.4 to 0.8).[23,24]

Modeling Results

There have been no prior modeling studies to inform the possible preventive effects of OCs on ovarian cancer incidence and mortality.

Biological Plausibility

The mechanisms underlying a potential protective effect of OCs on ovarian cancer risk are not entirely clear. One longstanding hypothesis ("the incessant ovulation theory") is that repetitive ovulations throughout reproductive life result in epithelial damage and repair cycles that subsequently increase the risk of developing ovarian cancer. Factors that decrease the number of ovulations such as pregnancies, breastfeeding, and use of OCs, therefore, are expected to reduce ovarian cancer risk.[25]

A protective effect of OCs may also be due to direct effects of the hormones on the ovarian epithelium, a theory that is supported by some biological evidence. First, the incidence of ovarian cancer is significantly elevated in poultry hens, which ovulate daily.[26] Second, in a 3-year study, macaque monkeys treated either with combination OCs or their individual estrogen or progestin components or with controls, a significant increase in apoptosis of the ovarian epithelium was demonstrated in the groups receiving progestins.[27] The apoptosis pathway preferentially eliminates cells that have sustained genetic damage.[28] The finding that progestins activate this critical pathway in the ovarian epithelium raises the possibility that progestin-mediated apoptotic effects, and not solely inhibition of ovulation, may be responsible for the reduction in ovarian cancer risk that is associated with OC use.[29] Finally, Schildkraudt et al. reported an increase in the protective effect of OCs when a high potency progestin was used.[29]

Although there are some biologically plausible mechanisms for a protective effect of OCs on ovarian cancer risk, recent pathogenetic data now suggest that many high-grade serous epithelial ovarian cancers arise not from the ovarian epithelium but from the distal fallopian tube.[30] Consistent with the epidemiologic data regarding OC use, prior work suggests that the fallopian tube epithelium is influenced by ovulatory cycles, with ovulation exerting an inhibitory effect.[31]

Rationale for Review

Although the evidence suggests that most women can take OCs safely,[32] the potential benefit of using OCs to reduce the risk of ovarian cancer must be weighed with knowledge of both the potential noncontraceptive health benefits of OCs[33,34] and their potential harms.[35-38] No comparative effectiveness analyses have been conducted to inform decisions about the use of OCs as a primary preventive strategy for ovarian cancer. Also, because the majority of evidence on noncontraceptive benefits and harms of OC use is derived from observational studies, careful consideration must be given to the potential biases inherent in those study designs when developing a research agenda and clinical recommendations. The combination of systematic review and decision-analytic modeling presented in this report allows us to estimate the tradeoffs between the harms and benefits of OC use for the overall population and for individual women, accounting for the potential influence of other factors.

Scope and Key Questions

Scope of Review

To evaluate the benefits and harms of the use of OCs as a primary preventive measure against ovarian cancer, we focused on synthesizing the available evidence for the effectiveness of this strategy in a general population and in groups at elevated risk. We also evaluated benefits and harms of OC use that are not related to the development of ovarian cancer. Finally, we designed a comparative effectiveness model to inform the questions generated by this review.

The scope of the review specifically excluded the unquestioned effectiveness of OCs in preventing unintended pregnancies; the potential effectiveness of OCs as primary or adjunctive treatments for conditions such as menstrual disorders (e.g., dysmenorrhea or menorrhagia), endometriosis, or premenstrual dysphoric disorder; and the potential role of OCs in preventing the onset of these conditions. For women considering the use of OCs for contraception or as treatment for symptomatic conditions, these effects are clearly the most important consideration. However, our overall focus was on the potential role of OCs as primary prevention for ovarian cancer. The overall clinical question we addressed was not, "What are the overall benefits and harms of OCs as a method of contraception or as treatment for certain conditions?"—a question that would require explicit comparisons of different contraceptive methods on all the relevant outcomes. Rather, the implicit question was, "Do the benefits and harms of OCs potentially justify their use *solely* as a primary preventive intervention (analogous to aspirin for the prevention of myocardial infarction) even in women who do not need contraception?"

Key Questions

With input from AHRQ, the CDC, and a Technical Expert Panel (TEP) of external stakeholders, we defined Key Questions using the general approach of specifying the population of interest, the interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods section for details). The Key Questions (KQs) considered in this systematic review were:

KQ 1: What is the effectiveness of combined (estrogen and progestin containing) and progestin-only oral contraceptives (OCs) for reducing the risk of ovarian cancer?

KQ 2: Do specifics of OC use (e.g., dose/formulation, age at initiation, duration of use) affect the relative risk of developing ovarian cancer?

KQ 3: Does the use of OCs by specific populations of women (e.g., those defined by age, family history of breast and ovarian cancer, BRCA1/BRCA2 mutation status, parity) affect the relative risk of developing ovarian cancer?

KQ 4: Aside from pregnancy prevention, are there other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

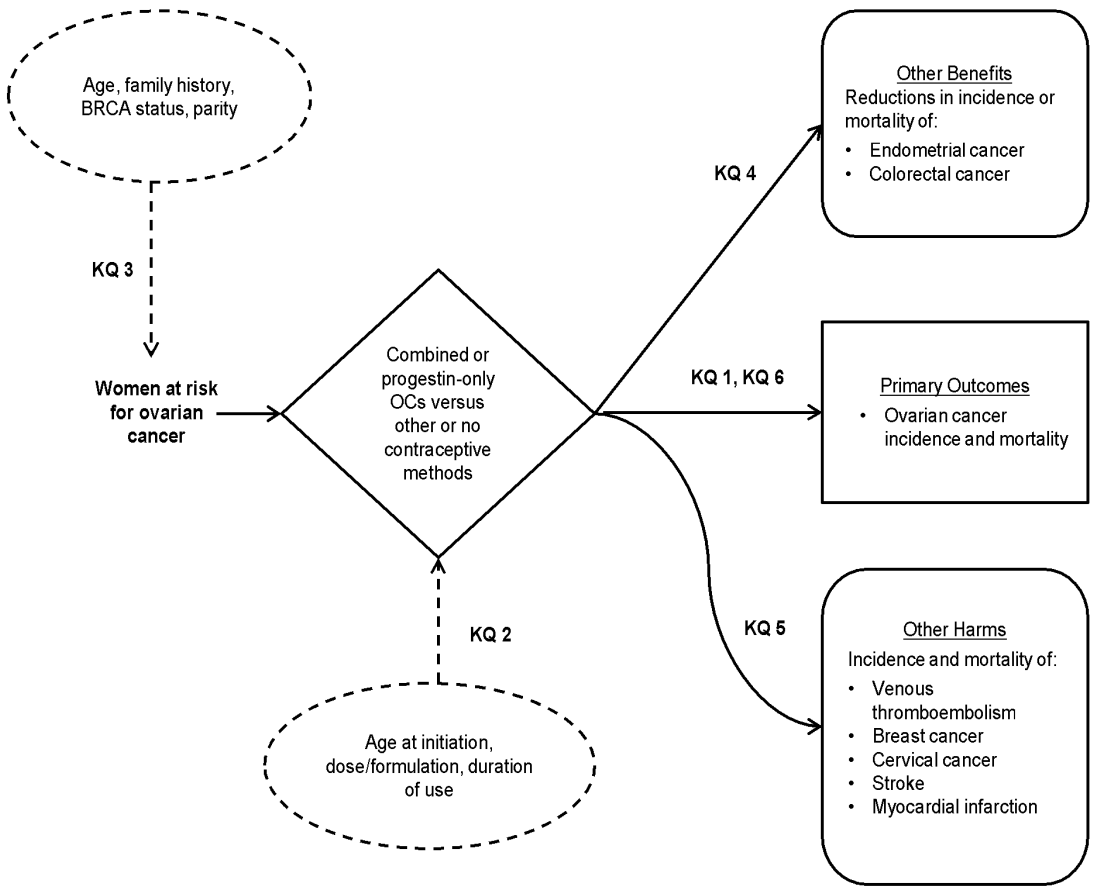
KQ 6: Based on the comprehensive literature review, what are the benefits and harms from the use of OCs to reduce the incidence of ovarian cancer for specific populations? Based on the decision model, what is the estimated effect of these benefits and harms on life expectancy and quality-adjusted life expectancy?

KQ 7: Based on the systematic review and decision model, what research gaps need to be filled to better understand whether OCs are effective for the primary prevention of ovarian cancer?

Analytic Framework

Figure 6 shows the analytic framework for this systematic review.

Figure 6. Analytic framework for systematic review



BRCA = breast cancer (genetic mutation); K = Key Question; OC = oral contraceptive
Note: KQ 7 is not shown in the analytic framework.

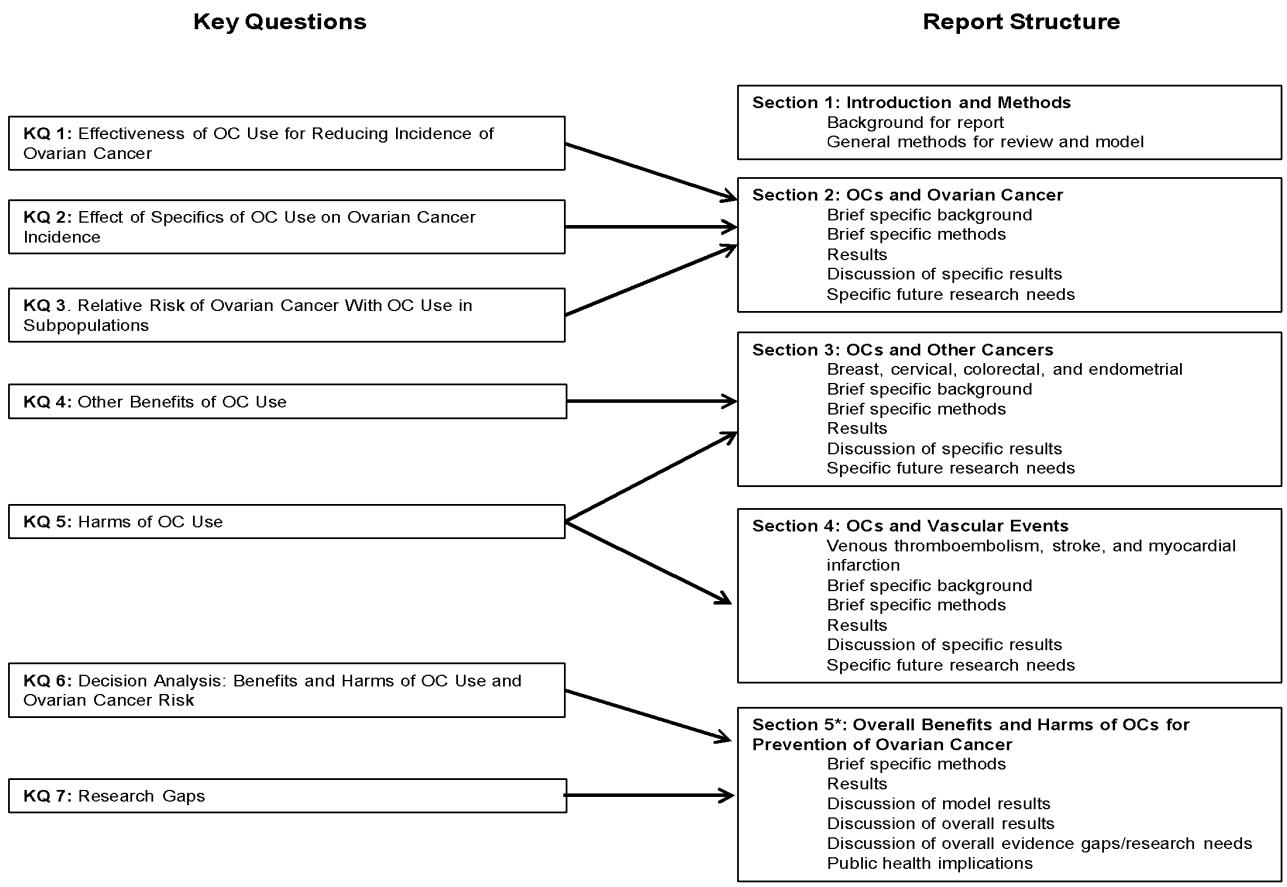
Organization of Report

This report departs from the standard AHRQ evidence report organization. The evidence is instead presented in four topic-focused sections. Figure 7 shows the relationship between the Key Questions and the report sections. Three of these sections address the relationship between OC use and specific groups of benefits and/or harms. The first such section, "Oral Contraceptives and Ovarian Cancer," focuses on ovarian cancer outcomes (KQ 1, KQ 2, and KQ 3); the second section, "Oral Contraceptives and Other Cancers," on breast, cervical, colorectal, and endometrial cancers (KQ 4 and KQ 5); and the third, "Oral Contraceptives and Vascular Events," on venous thromboembolism, stroke, and myocardial infarction (KQ 5). Within each section, the benefits and/or harms of OC use are considered for both the general population and specific populations of women for whom the risk levels of ovarian cancer are elevated. Where possible, our analyses also consider potential modifying factors such as dose, formulation, and

duration of OC use. Each section also considers specific evidence gaps and needs for future research regarding the association between OC use and the specific outcomes (KQ 7).

The final section of the report, "Overall Benefits and Harms of Oral Contraceptives for Prevention of Ovarian Cancer," uses a decision analytic framework to explore the overall benefits and harms of all outcomes considered in the report. In this section, we present the results of our comparative effectiveness decision model, considering the overall effect of OC use on benefits and harms for both the general population and specific populations of women at varying levels of risk (KQ 6). In this final section, we also use the modeling framework to identify additional evidence gaps and needs for future research related to the potential overall benefits and harms of OCs for prevention of ovarian cancer (KQ 7).

Figure 7. Report roadmap



KQ = Key Question; OC = oral contraceptive
*Note that Section 5 also summarizes the Key Questions.

Methods

The methods for this evidence report follow those suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the "Methods Guide").[39] The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.[40] All methods and analyses were guided by a review protocol, which was developed as described below.

Review Protocol

At the outset of this review, the Key Questions were defined collaboratively with input from AHRQ, the CDC, and the TEP. The TEP comprised individuals representing medical professional societies/clinicians in the areas of obstetrics, gynecology, reproductive health, and gynecologic oncology; Federal health agencies with an interest in cancer care/prevention, oral contraceptive benefits/harms, and women's health research; scientific and methodological experts; a nonprofit cancer advocacy organization; and representatives of ovarian cancer patient and women's reproductive health groups. The TEP was convened to provide input in defining populations, interventions, comparisons, and outcomes; considering potential analysis and modeling approaches; and aiding in identifying particular studies or databases to search. Members of the TEP were required to disclose any relevant business or professional conflicts of interest and any financial conflicts of interest greater than $10,000. Potential conflicts of interest were balanced or mitigated. Members of the TEP did not perform analyses of any kind and did not contribute to the writing of the report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input, reviewed by AHRQ and the CDC, and posted for public access at the AHRQ Effective Health Care Web site.[41]

Literature Search Strategy

Search Strategy

We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews to identify relevant literature published from January 1990 to June 2012. Our search strategies used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. We date-limited our searches to articles published since January 1990 because, given the lag time between OC exposure and subsequent ovarian cancer development, much of the older literature concerning OC use and ovarian cancer is based on OC formulations that are no longer on the market. In addition, many of the other benefits and harms of OC use are observed within several years of initial use. Restricting the search to 1990 forward increases the likelihood that the types of OCs used by the women in the studies we retrieved were similar to those currently available, and thus aids in maximizing the generalizability and clinical relevance of the results. In addition to the databases listed above, we also searched ClinicalTrials.gov to identify additional relevant articles from completed studies. Search dates and exact search strings for all searches are provided in Appendix A. All searches were designed and conducted in collaboration with an experienced search librarian.

We supplemented the electronic searches with a manual search of citations from a set of key review articles.[42-67] The reference lists from these articles were hand-searched and cross-referenced against our library of database search results. Additional relevant articles not already under consideration were retrieved for screening. All citations were imported into an electronic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA). We did not systematically search gray literature databases beyond our review of potentially relevant studies listed in ClinicalTrials.gov—the high volume of literature identified through our searches of peer-reviewed articles made it unlikely that further searching of gray literature would substantially increase the chances of identifying relevant data that would meet inclusion criteria. However, we did invite additional information through a request for scientific information packets that was submitted to drug manufacturers on our behalf by AHRQ. Submissions received through this mechanism were reviewed and relevant citations screened against the review inclusion/exclusion criteria.

Inclusion and Exclusion Criteria

The PICOTS-based criteria developed to screen articles for inclusion/exclusion at the title/abstract and full-text levels are detailed in Table 1.

Table 1. Summary of inclusion and exclusion criteria for the systematic review

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• All KQs: ○ Women taking OCs for contraception or women taking OCs for primary prevention of ovarian cancer[a] ○ Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy • KQs 3 and 6: ○ Women with a family history of ovarian or premenopausal breast cancer suggesting increased risk based on current recommendations ○ Women with a known BRCA1/BRCA2 mutation	Nonhuman studies
Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	Study does not provide a description of at least one of the following: (1) OC formulation(s) used (2) Length of OC use (Not required for studies reporting ovarian cancer outcomes or conducted in a population taking OCs for primary prevention of ovarian cancer)
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Study does not include controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable) Studies comparing OC formulations (without including a non-OC control) are acceptable for studies reporting venous thromboembolism, stroke, or MI outcomes

Table 1. Summary of inclusion and exclusion criteria for the systematic review (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria

Outcomes	Study reports quantitative association between exposure to OCs and one of the outcomes listed below:
	• KQs 1, 2, 3, 6:
	  ○ Diagnosis of ovarian cancer, ovarian cancer mortality
	  ○ Adverse effects (see KQ 5)
	• KQ 4:
	  ○ Diagnosis of endometrial cancer, endometrial cancer mortality, diagnosis of colorectal cancer, colorectal cancer mortality
	  ○ Adverse effects (see KQ 5)
	• KQ 5:
	  ○ Diagnosis of breast cancer, cervical cancer, venous thromboembolic event, stroke, or myocardial infarction; disease-specific mortality associated with these outcomes
	• KQ 7: Not applicable
		Study only reports outcomes related to assisted reproductive technologies or abortion

Timing	Studies of any duration	None
Setting	All settings	None
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, non–systematic review, or letter to the editor) • Exploratory study with inadequate sample size

Publications	• English-language only
	• Peer-reviewed articles
	• Outcome reporting falls within the following publication ranges:
	  ○ Study reports an ovarian cancer outcome of interest and was published on or after 01-Jan-1990[d]
	  ○ Study reports a breast, endometrial, cervical, or colorectal cancer outcome of interest and was published on or after 01-Jan-2000[e]
	  ○ Study reports a venous thromboembolic event, stroke, or myocardial infarction outcome of interest and was published on or after 01-Jan-1995[f]
		Non-English articles[g]

KQ=Key Question; MI = myocardial infarction; OC=oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from direct abstraction; those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies <100 subjects were excluded because confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]We considered studies published from January 2000 to June 2012 for the primary ovarian cancer outcome analyses. Older data (with publication dates beginning January 1990) were used to conduct sensitivity analyses allowing us to compare the results from the January 2000 to June 2012 analyses with those from a longer date range (January 1990 to June 2012).

[e]Date ranges for these cancer outcomes were selected to balance generalizability (OC formulations used in earlier studies not currently on market) and power (peak incidence of cancers 10 to 30 years after typical use of oral contraceptives).

[f]Date ranges for acute vascular events associated with OC use were restricted to more recent years to reflect currently available formulations.

[g]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies) and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Study Selection

Using the inclusion and exclusion criteria described in Table 1, two investigators independently reviewed the titles and abstracts of articles retrieved through the search strategies for potential relevance to the KQs. Articles included by either reviewer were promoted to full-text screening. At the full-text screening stage, two investigators independently reviewed the full text of each article and indicated a decision to include or exclude the article for data abstraction. When paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, we reconciled the difference through review and discussion among investigators. Articles meeting eligibility criteria were included for data abstraction. All screening decisions were made and tracked in a Distiller SR database (Evidence Partners Inc., Manotick, ON, Canada).

Data Extraction

The investigative team created forms for abstracting the data elements for the KQs. The abstraction forms were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors for accuracy. Based on clinical and methodological expertise, pairs of researchers were assigned to abstract data from the eligible articles. One researcher abstracted the data, and the second reviewed the completed abstraction form alongside the original article to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus could not be reached by the first two researchers.

To aid in both reproducibility and standardization of data collection, guidance documents were drafted and given to the researchers as reference material, and researchers received further data abstraction instructions directly on each form created specifically for this project within the DistillerSR data synthesis software. We designed the data abstraction forms for this project to collect information required to conduct the review, including data needed to evaluate the specified eligibility criteria for inclusion; demographic and other patient characteristics of relevance (e.g., family history of ovarian cancer); details of the interventions and comparators (e.g., OC dose, formulation, patterns of use); outcome measures and adjustment factors applied in study analyses; and data needed to assess quality and applicability. Appendix B provides a detailed listing of the data elements abstracted.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the approach described in AHRQ's "Methods Guide."[39] To assess quality, we used the approach to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. To evaluate methodological quality, we applied criteria for each study type derived from core elements described in the "Methods Guide." Criteria of interest for all studies included similarity of groups at baseline, the extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, and conflicts of interest. No randomized controlled trials were identified for inclusion in this review, thus criteria specific to randomized studies (e.g., methods of randomization and allocation concealment) were not considered.

Additional elements considered for observational studies included methods for selection of participants and management of selection bias, measurement of interventions/exposures,

addressing any design-specific issues, and controlling confounding. To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, and poor (Table 2). For each study, one investigator assigned a summary quality rating, which was then reviewed by a second investigator; disagreements were resolved by consensus or by a third investigator if agreement could not be reached. Several studies are represented by more than one article. In some of those cases, the study data could not be combined into one abstraction. In those instances, the quality ratings for individual abstractions within a study grouping could vary based on the specific component articles' quality of reporting, the evaluated outcomes, and the statistical and analytical methods used.

Table 2. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. In addition, specific to cohort and case-control studies, inclusion/exclusion criteria were applied consistently to all comparison groups; cases and controls were selected appropriately; strategies for recruiting patients were consistent across study groups; and confounding variables were assessed using valid and reliable measures and implemented consistently across all study participants.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Data Synthesis

We used two complementary approaches to data synthesis. First, we summarized the primary literature by abstracting relevant continuous (e.g., age and categorical data (e.g., BRCA1/2 mutation status). We then determined the feasibility of completing a quantitative synthesis. Feasibility generally depended on the volume of relevant literature, the conceptual homogeneity of the studies, and the completeness of the reporting of results. For this topic, meta-analysis was particularly challenging, because (1) all of the literature was observational, increasing the methodological complexity of the meta-analysis, and (2) there was substantial heterogeneity in the types of exposures (e.g., OC formulation), timing of exposures (e.g., intermittent use of OCs over the course of a reproductive lifetime) and how exposures were measured and reported (ever users versus never users or current versus noncurrent users, duration of use as a continuous or categorical variable). Despite the challenges, we determined that meta-analysis was indicated for a number of the outcomes of interest considered in this review; other outcomes for which meta-analysis was not feasible are summarized using descriptive statistics.

Even when meta-analysis was feasible, at best the results provide evidence for whether there is an association between OC use and a specific outcome, the direction of that association (toward harm or benefit), and the magnitude and precision of that association, which allows estimation of the probability of developing that outcome in OC users *relative* to nonusers.

Estimating the impact of the association on the *absolute* probability of developing that outcome, for either an individual or a population, requires additional methods. First, in order to estimate the absolute increase or decrease in risk based on the results of the meta-analysis, we used the results of the meta-analyses, together with data on the overall incidence of the outcome and the prevalence of OC use, to estimate age-specific incidence in ever versus never users (for cancer outcomes) and current versus noncurrent users (for acute vascular events). Although these results are useful for estimating the risk of individual outcomes, they do not account for the interaction of multiple competing risks, including both the outcomes of interest and other events, such as death from other causes or surgical removal of the ovaries for benign conditions, that affect the overall impact of OC use at the individual and population level. In order to estimate these joint effects, we developed a comparative effectiveness decision model that allowed us to simulate the joint effects of OC use on cancer and vascular events on the overall balance of benefits and harms. The model also allows exploration of the effects of variation in different aspects of OC use (such as age at first use, duration of use, or individual risk of various outcomes) on the overall impact of OC use. Finally, the model allows estimation of uncertainty in the individual estimates of OC effects on overall uncertainty about the balance of benefits and harms, which in turn may help prioritize future research needs.

Outcome Measures

For each disease/condition of interest, we estimated the effect of OC use on a number of outcomes. Outcome measures considered for the meta-analyses were:

- Disease-specific incidence (i.e., were OC users more or less likely to develop the disease/condition?)
- Disease-specific mortality (i.e., were OC users more or less likely to die from a given cause than nonusers?)
- Disease-specific survival (i.e., among women who developed the outcome, were OC users more or less likely to die than nonusers?)

The following outcome measures were considered for modeling:

- Age-specific incidence
- Cumulative lifetime incidence
- Cumulative lifetime mortality from outcomes
- Life expectancy
- Quality-adjusted life expectancy
- Number needed to harm and number needed to prevent (derived from absolute differences in lifetime incidence and mortality)
- Harm/benefit ratio for disease incidence (defined as the sum of excess cases of breast cancer, cervical cancer, myocardial infarction, deep venous thrombosis, pulmonary embolism, and stroke in OC users, divided by the sum of prevented cases of ovarian, colorectal, and endometrial cancers); each cancer also was considered individually
- Harm/benefit ratio for disease mortality (defined as the sum of excess deaths from breast cancer, cervical cancer, myocardial infarction, deep venous thrombosis, pulmonary embolism, and stroke in OC users, divided by the sum of prevented deaths from ovarian, colorectal, and endometrial cancers); each cancer also was considered individually

Meta-Analytic Methods

Details of the specific approaches to the meta-analysis of the effects of OC use on ovarian cancer, other cancers, and acute vascular events are provided in the relevant sections. Our general approach for each outcome was to analyze, if possible, the following associations:

- Temporal relationships:
  - Ever versus never OC use
  - Current versus noncurrent OC use
  - Duration of current OC use
  - Age at first OC use
  - Time since last OC use
- OC formulation:
  - Estrogen dose (high versus low)
  - Progestin generation (first, second, third, and fourth generations)
- Special populations (such as women with known family history or genetic predisposition)

When study designs and outcomes reported were similar and the population in the study was broad (e.g., not Factor V Leiden carriers), we estimated pooled odds ratios with 95% confidence intervals (95% CIs) using a random-effects model. We evaluated heterogeneity visually and with the Cochran *Q* statistic using a threshold p-value of less than 0.10. We stratified analyses by study type (case-control, cohort, pooled analyses). All meta-analyses were performed using Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ; 2005).[68]

Confidence intervals from the included study publications were entered into the Comprehensive Meta-Analysis (CMA) program. However, many of these confidence intervals had been rounded to a single decimal place. The CMA program checks the intervals for symmetry in the logarithmic scale. In certain cases, the rounded limits were not accepted by CMA. In such cases, we kept the point estimate as given but changed the confidence limits so that they were symmetric. This resulted in slight differences in the confidence intervals in the forest plots when compared with the study publications.

Results were discussed qualitatively when study numbers were insufficient for meta-analysis (less than three), when confidence intervals around measures of association were not reported or could not be calculated, or when a study included a special population that is not likely to be representative of the general population of reproductive age women.

We included data from pooled analysis articles in our meta-analyses if all three of the following conditions were met:

- None of the individual studies included in the pooled analysis had already been included for meta-analysis.
- At least half of the studies in the pooled analysis were published on or after the date threshold applied for the outcome under consideration in the analysis (January 1, 2000, for ovarian cancer outcomes; January 1, 2000, for other included cancer outcomes; and January 1, 1995, for acute vascular events)
- Data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

Estimation of Absolute Risks

We estimated the impact of OC use on age-specific absolute risk from population-based estimates of age-specific incidence, age-specific exposure estimates for OCs, and the derived odds ratios from the meta-analyses. For any outcome,

Overall Incidence = (Incidence in OC users) * (Prevalence OC use) + (Incidence in nonusers) * (Prevalence nonuse).

since

Incidence in OC users = (Incidence in nonusers) * (Relative risk in OC users),

and

Prevalence nonuse = 1 – (Prevalence OC use),

separate estimates for age-specific incidence in users and nonusers can be derived from the overall incidence, the prevalence of OC use, and the relative risks (estimated here from the odds ratios from the respective meta-analyses).

Simulation Model

We constructed a semi-Markov state-transition model that modeled a cohort of women aged 10 to 100, using TreeAge Pro 2012 (Williamstown, MA: TreeAge, Inc.). Age-specific and race-specific probabilities of OC use and important competing risks or effect modifiers, such as all-cause mortality, tubal ligation, hysterectomy, and oophorectomy, were obtained from the literature or publicly available data sources. Estimates for the effect of OC use on cancers and vascular events were based on the results of the meta-analysis, based on either ever or current use of OCs. Other factors, such as duration of use, were included if they were statistically significant in the meta-analysis.

The model was run as a microsimulation, which allowed conditioning of probabilities on past history. Depending on the analysis, each model run included 5,000 to 1,000,000 simulated individuals, with estimates of the outcomes of interest based on the mean value of each model run (or, in some cases, the weighted average of multiple model runs).

Estimates were derived for both the overall population given current OC use patterns (i.e., the cumulative effect of current patterns of age of starting OCs and duration of use on the outcomes of interest based on the risk estimates compared with a scenario where OCs had no effect on risk), as well as at the individual level (the cumulative effect of OC use in all users, based on current patterns of use, vs. nonusers).

The impact of varying age of starting and duration of use was assessed in a separate analysis.

Finally, we assessed the impact of uncertainty in the estimates of OC effects by using a method analogous to cost-effectiveness analysis, where total harms were considered as “costs” and assessing the effect of uncertainty in the effects (based on the confidence intervals of the relative risk estimate) on whether OC use would be recommended based on different “willingness-to-pay” thresholds for harm/benefit ratio.

Strength of Evidence

The strength of evidence for each Key Question and outcome was assessed using the approach described in the "Methods Guide."[39,69] The evidence was evaluated using the four required domains (Table 3).

Table 3. Strength of evidence required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Assessed primarily through study design (RCT vs. observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of "no effect" and the overall range of effect sizes
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons (e.g., direct comparison of stroke risk in women using OCs compared with women using IUDs) or indirect comparisons through use of surrogate outcomes (e.g., measurement of blood-clotting factors in women using OCs vs. IUDs) or use of separate bodies of evidence (risk of stroke in OC users vs. placebo, and risk of stroke in IUD users vs. placebo)
Precision	Precise Imprecise	Based primarily on the size of the confidence intervals of effect estimates

IUD = intrauterine device; OC = oral contraceptive; RCT = randomized controlled trial

Additionally, when appropriate, the studies were evaluated for dose-response association, the presence of confounders that diminished an observed effect, strength of association (magnitude of effect), and publication bias. The strength of evidence was assigned an overall grade of high, moderate, low, or insufficient according to the following four-level scale:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

Applicability

To assess applicability, we used the PICOTS format to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the "Methods Guide."[39,70] We used data abstracted on the population studied, the intervention and comparator, the outcomes measured, study settings, and timing of assessments to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the "Methods Guide."

Specific factors affecting applicability included (but were not limited to):

- Population: We anticipated that most of the literature was based on women using OCs for contraception, not as prevention for ovarian cancer. Factors such as parity and BRCA status, which affect underlying ovarian cancer risk, may differ (or not be reported) compared with current relevant groups. The balance of other benefits and harms (particularly cardiovascular and thrombotic risks) may differ based on age of use, which would be relevant in some subpopulations (e.g., women over 35 who have not previously used OCs).
- Intervention and comparator: The formulation of OCs used in the literature may not reflect currently available OCs, and the duration and pattern of use may not reflect potential duration and pattern in the setting of primary ovarian cancer prevention. Currently available alternatives to OCs may not have been included in "nonuser" groups in the literature.
- Outcomes: Data on all the relevant outcomes is unlikely to be available for all potentially applicable comparators, particularly newer contraceptive methods.

We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively throughout the sections of the report.

Peer Review and Public Commentary

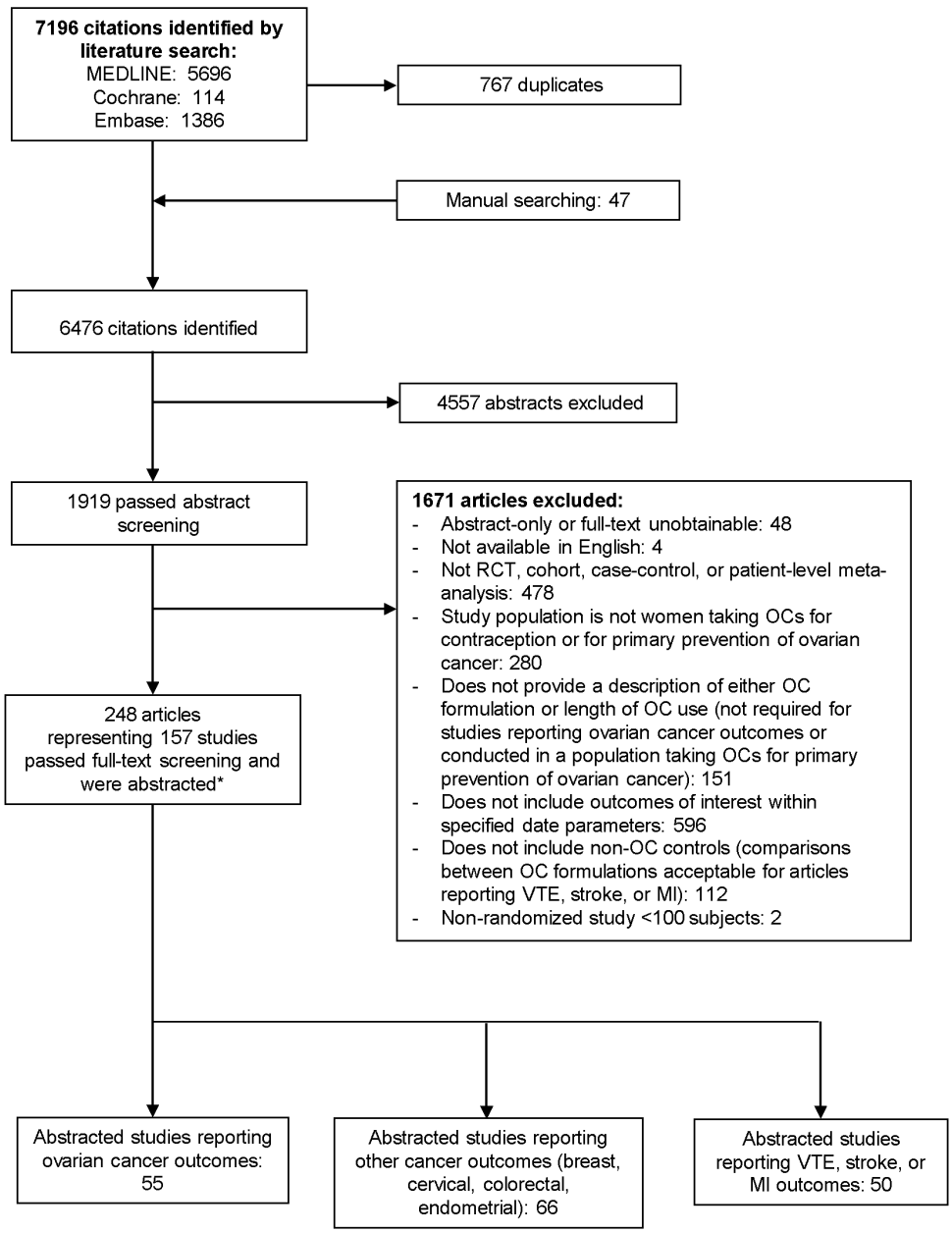
The peer review process is our principal external quality-monitoring device. Experts in key clinical and research areas (obstetrics/gynecology; gynecologic oncology; prevention, screening, treatment, and management of gynecologic cancers; chemoprevention of cancer; women's health), methodological areas (cancer epidemiology, decision modeling, systematic review), along with individuals representing ovarian cancer patient interest communities and women's reproductive health stakeholders were invited to provide external peer review of this draft report. AHRQ, CDC representatives, and an associate editor provided comments, as did members of the Technical Expert Panel. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented our responses in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site.

Literature Search Results

In Figure 8, we depict the flow of articles through the literature search and screening process for the review as a whole. Searches of PubMed, Embase, and the Cochrane Database of Systematic Reviews yielded 7,196 citations, 767 of which were duplicates. Manual searching and contacts to drug manufacturers identified 47 additional citations, for a total of 6476. No additional relevant citations beyond those already identified were found from a search for relevant studies listed on ClinicalTrials.gov. After applying inclusion/exclusion criteria at the title-and-abstract level, 1919 full-text articles were retrieved and screened. Of these, 1671 were excluded at the full-text screening stage, leaving 248 articles (representing 157 unique studies) for data abstraction. As indicated in Figure 8, several articles/studies were relevant to more than one outcome of interest (55 relevant to ovarian cancer outcomes (KQ 1, KQ 2, KQ 3), 66 to other cancers of interest (KQ 4, KQ 5), and 50 to vascular events (KQ 5).

Subsequent sections of this report describe the key points of the findings, summaries of the included studies relevant to each section, and a detailed synthesis of the evidence. Appendix C provides full citations of included articles as well as the relationship between related articles for the same study/patient population. Note that in the descriptive portions of the text, related data from articles considered to be part of one study grouping may be represented in both the case-control and cohort categories (if both designs are applicable) due to a relationship between the represented patient populations. Similarly, related data from articles considered to be part of one study grouping may be represented in more than one quality category (see the Methods section for a full description of quality assessment). Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 8. Literature flow diagram



MI = myocardial infarction; OC = oral contraceptive; RCT = randomized controlled trial; VTE = venous thromboembolism
*Note that a given study may address more than one outcome group.

Section 2. Oral Contraceptives and Ovarian Cancer

Background

Ovarian cancer has a lifetime incidence of about 1.4 percent and kills over 15,000 women in the United States annually.[1] While the concept of an early detection strategy is attractive for this disease, no screening strategy has yet been proven effective.[10] The stage distribution is weighted heavily toward Stage III and IV disease, suggesting that most ovarian cancers progress rapidly; indeed, a growing body of evidence suggests that many epithelial ovarian cancers initially arise in the epithelium of the fallopian tube. Based on this and pathogenetic evidence, the underlying biology of the disease may limit the potential effectiveness of screening to reduce morbidity and mortality from ovarian cancer.[12,71] Alternative strategies, including the use of novel therapies and primary prevention, need to be considered and evaluated.

Primary Prevention Strategies

Prevention strategies, including surgical prophylaxis and chemoprevention, may be of particular interest to women who are at an elevated risk of ovarian cancer due to a strong family history or a known inherited genetic mutation. Women who are carriers of genetic mutations in BRCA1 or BRCA2 are at markedly increased risk for ovarian cancer. A pooled analysis of 22 studies estimated the average risk of developing ovarian cancer by age 70 is 39 percent (95% confidence interval [CI], 18% to 54%) for BRCA1 mutation carriers and 11 percent (CI, 2.4% to 19%) for BRCA2 mutation carriers.[72] Likewise, women with Lynch syndrome–associated MLH1 and MSH2 mutations have 20 percent (CI, 1% to 65%) and 24 percent (CI, 3% to 52%) risk, respectively, of developing ovarian cancer by the same age.[73] Although the prevalence of genetic mutations predisposing women to ovarian cancer in the general population is low (approximately 0.12% for BRCA1 and 0.2% for BRCA2),[74] the high risk of cancer among women who are mutation carriers underscores the importance of understanding factors that may modify their likelihood of developing cancer.

Oral contraceptives (OCs) represent a potentially promising primary prevention strategy for ovarian cancer. Several large pooled analyses suggest that OCs confer a protective effect on ovarian cancer risk, with a reduction in risk of up to 50 percent with long-term use of OCs.[21-24] The largest pooled analysis to date estimates that OC use has already prevented 200,000 cases of ovarian cancer and 100,000 deaths from this disease worldwide.[21]

In women at high risk of developing ovarian cancer due to family history or a known genetic mutation, the effect of OC use on ovarian cancer risk is relevant for multiple reasons. First, the incomplete penetrance of hereditary cancer genes suggests that there are other factors—either environmental or genetic—that affect whether or not women who are mutation carriers develop ovarian cancer. Thus, from an etiologic standpoint, it is important to understand whether a common environmental exposure such as OCs influences the risk of developing ovarian cancer among mutation carriers. Second, women who are at high genetic risk have a need to understand the options available for reducing morbidity and mortality from ovarian cancer.

The choice of a risk-reduction strategy for women at elevated risk is an individual choice and commonly includes screening strategies and prophylactic surgery. Unfortunately, screening high-risk women with available modalities has not yet proven successful.[75-77] In a BRCA1/2 mutation–carrying population, bilateral salpingo-oophorectomy (BSO) has been demonstrated to reduce the risk of ovarian, tubal, or peritoneal cancers by 80 percent and the risk of breast cancer

by 50 percent.[14] In addition, several groups have used health-economic decision models to suggest that prophylactic surgery is both effective and cost-effective in the BRCA carrier population.[15,16] However, surgical prophylaxis is accompanied both by potential harms and the certain premature loss of ovarian function. Despite the effectiveness of prophylactic BSO, some women at high risk prefer alternatives that are less invasive, do not result in early menopause, and preserve fertility. The Gynecologic Oncology Group is currently completing a nonrandomized prospective trial comparing longitudinal screening with CA-125 and ultrasound to risk-reducing BSO in a high genetic risk population.[78] This trial includes both subsequent cancer diagnoses and quality-of-life assessments and may be informative from a comparative effectiveness standpoint.

Chemoprevention may be a viable option for ovarian cancer risk reduction, and particularly among women at high genetic risk. If OCs confer a comparable reduction in ovarian cancer risk in genetic mutation carriers as that observed in the general population, they could be a reasonable chemoprevention strategy for those who have not completed childbearing or who wish to avoid surgery.

In Section 2 of our systematic review and meta-analysis, we quantify the potential benefits of OC use in reducing the incidence of ovarian cancer. We address the effect of OCs on ovarian cancer risk, both in the general population and in specific populations of interest, as well as examining relationships between specific characteristics of OC use and ovarian cancer incidence and mortality.

Relevant Key Questions

The seven KQs developed for the entire systematic review are listed in Section 1 (refer to Figure 7 for a roadmap of this report). For Section 2, we performed a systematic review and meta-analysis of three of the seven KQs that address the effectiveness of OCs in reducing the risk of developing ovarian cancer:

KQ 1: What is the effectiveness of combined (estrogen and progestin containing) and progestin-only OCs for reducing the risk of ovarian cancer?

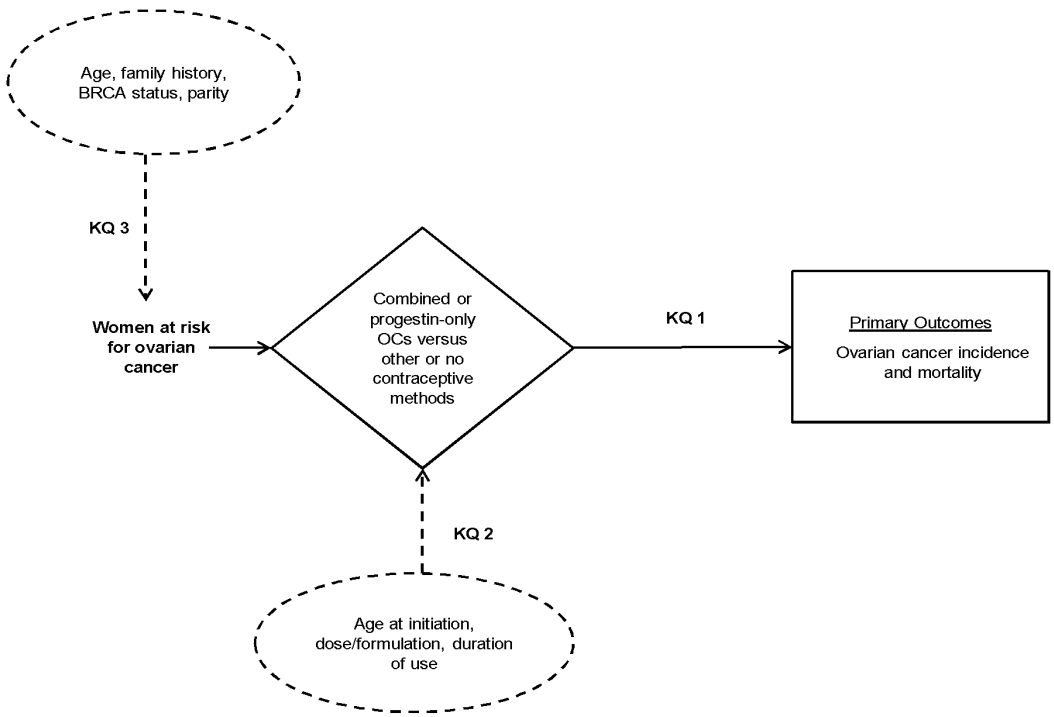
KQ 2: Do specifics of OC use (e.g., dose/formulation, age at initiation, duration of use) affect the relative risk of developing ovarian cancer?

KQ 3: Does the use of OCs by specific populations of women (e.g., those defined by age, family history of breast and ovarian cancer, BRCA1/BRCA2 mutation status, parity) affect the relative risk of developing ovarian cancer?

Analytic Framework

Figure 9 shows the analytic framework that guided this section of the review.

Figure 9. Analytic framework for OCs and ovarian cancer



BRCA = breast cancer genetic mutation; KQ = Key Question; OC = oral contraceptive

Methods

Inclusion and Exclusion by PICOTS

Table 4 describes the PICOTS criteria that guided the literature search for this section of the review.

Table 4. Summary of inclusion and exclusion criteria for OCs and ovarian cancer

Study Characteristic	Inclusion Criteria	Exclusion Criteria

Population	• All KQs
	  ○ Women taking OCs for contraception or women taking OCs for primary prevention of ovarian cancer[a]
	  ○ Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy
	• KQ 3:
	  ○ Women with a strong family history of ovarian or premenopausal breast cancer
	  ○ Women with a known BRCA1/BRCA2 mutation
		Nonhuman studies

Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	None
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Study does not include controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable)
Outcomes	Study reports quantitative association between exposure to OCs and either ovarian cancer incidence or ovarian cancer mortality	Study only reports outcomes related to assisted reproductive technologies or abortion
Timing	Studies of any duration	None
Setting	All settings	None
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, non–systematic review, letter to the editor) • Exploratory study with inadequate sample size
Publications	• English-language only • Peer-reviewed articles • Study reports an ovarian cancer outcome of interest and was published on or after 01-Jan-1990[d]	Non-English articles[e]

KQ = Key Question; OC = oral contraceptive

[a]If the purpose of OC use was unclear, it was assumed to be contraception.

[b]Systematic reviews and study-level meta-analyses were excluded from abstraction; those representing key sources were hand-searched as potential sources of additional material.

[c]Small nonrandomized studies <100 subjects were excluded as confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.

[d]We considered studies published from January 2000 to June 2012 for the primary ovarian cancer outcome analyses. Older data (with publication dates beginning January 1990) were used to conduct sensitivity analyses allowing us to compare the results from the January 2000 to June 2012 analyses with those from a longer date range (January 1990 to June 2012).

[e]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies) and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Meta-Analytic Methods

To examine quantitatively the effect of OCs on the risk of ovarian cancer, we performed meta-analyses on the following relationships:

- Ever OC use
- Temporal relationships:
  - Duration of OC use
  - Age at first OC use
  - Time since last OC use
- OC formulation:
  - Estrogen
  - Progestin
- Special populations:
  - BRCA1 and BRCA2 genetic mutation carriers
  - Family history
  - Parity/gravidity

To perform a meta-analysis, we required that at least three individual studies address the relationship in question. Each included study must also report odds ratios and either report 95 percent confidence intervals (95% CIs) or provide sufficient data to allow us to calculate the 95% CI describing the relationship. We performed meta-analyses using Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ; 2005).[68] All analyses were done using a random-effects model.

Confidence intervals from the included study publications were entered into the Comprehensive Meta-Analysis (CMA) program. However, many of these confidence intervals had been rounded to a single decimal place. The CMA program checks the intervals for symmetry in the logarithmic scale. In certain cases, the rounded limits were not accepted by CMA. In such cases, we kept the point estimate as given but changed the confidence limits so that they were symmetric. This resulted in slight differences in the confidence intervals in the forest plots when compared with the study publications.

Pooled Analyses

We included pooled analyses in our meta-analyses if all three of the following conditions were met:

1. None of the individual studies included in the pooled analysis had already been included for meta-analysis.
2. At least half of the studies in the pooled analysis were published on or after January 1, 2000.
3. Data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

Ever OC Use

For the primary ever OC use meta-analysis, we excluded studies that reported effects for only a particular subpopulation (e.g., studies reporting odds ratios only for women with a BRCA mutation) but not the effects for the general population. (Separate analyses were performed for the subpopulations of BRCA mutation carriers and are described below.) Studies that reported ever OC use odds ratios for two or more mutually exclusive subpopulations (e.g., mucinous and

nonmucinous tumors) were included in the meta-analysis, and results for the subpopulations were combined.

Temporal Relationships

Evaluation of clinical relationships for which multiple temporal stratifications were possible—such as duration of OC use, age at first OC use, and time since last OC use (recency)—required creation of several additional simplifying assumptions:

- To facilitate identification of any existing dose-response or duration-response effects, we included only studies that reported odds ratios for at least three different time intervals. Studies that had a median split often had that split in the first interval. Thus, the rate for the upper half would be used to help estimate the rate for all three intervals. It seemed as if this would dilute any dose-response relationship.
- We required that the odds ratios were reported relative to no OC use.

Duration of OC Use

The challenge of performing a meta-analysis on duration of OC use is that individual studies reported the odds ratios for different duration intervals. Simplifying assumptions for this analysis are listed above. We assumed that each odds ratio, OR_{ij}, could be described by the following model:

$$Ln\left[OR_{ij}\right]=\alpha_i+\sum_{j=1}^{k} x_{ij}\,\beta_j,$$

where i denotes the study, j denotes the specific time interval, and k is the number of time intervals used in the model. The α_i are assumed to be random and normal with mean 0 and variance $(SE_{ij}^2 + \sigma^2)$. SE_{ij} is the standard error of the j^{th} odds ratio from the i^{th} study. σ^2 is the extra variation from the random effects model. The x_{ij} are the fixed terms that describe the time period covered by that particular odds ratio. The β_j ($j=1, \ldots, k$) are the odds ratios to be estimated for each duration interval.

We originally assumed that there was a term for each year (up to 10) and a final term for greater than 10 years. However, the large number of terms resulted in very unstable estimates. For that reason, we broke the time points into 4 intervals: (1) 1 to 12 months, (2) 13 to 60 months, (3) 61 to 120 months, and (4) more than 120 months. We then used the x_{ij} to create the time period desired. For example, if the first interval were from 1 to 36 months, then the vector of x_{ij} would be (1/3, 2/3, 0, 0, 0). This would reflect that one-third of the patients in the interval were in the 1 to 12 month interval and two-thirds of the patients were in the 13 to 60 month interval. Using this methodology, any interval could be described.

The model was fitted using SAS PROC NLMIXED (SAS Institute Inc.; Cary, NC; 2009) with "subject" set to the particular study, i.

Age at First OC Use

Using the equation above, we assumed that there were only four different intervals for age at first use: (1) under 20 years of age, (2) 20 to 24 years of age, (3) 25 to 30 years of age, and (4) over 30 years of age. We then used the x_{ij} to create the time period desired. For example, if the second interval from a particular study were from 20 to 28 years of age, then the vector of x_{ij} would be (0, 1/2, 1/2, 0, 0). This would reflect that half the patients in the interval were in the 20

to 24 year interval and half the patients were in the 25 to 30 year interval. Using this methodology, any interval could be described.

Time Since Last OC Use

Using the equation above, we broke time since last OC use into 4 intervals: (1) 0 to 10 years, (2) 10 to 20 years, (3) 20 to 30 years, and (4) more than 30 years. We then used the x_{ij} to create the time period desired. For example, if the first interval were from 1 to 15 years, then the vector of x_{ij} would be (2/3, 1/3, 0, 0, 0). This would reflect that two-thirds of the patients in the interval were in the 0 to 10 year interval and one-third of the patients were in the 10 to 20 year interval. Using this methodology, any interval could be described.

OC Formulation

Estrogen

Studies were included in the meta-analysis if they reported the effect of low-dose and/or high-dose estrogen-containing OCs on ovarian cancer incidence and included methodology regarding the definition of low- and high-dose estrogen.[79,80] For studies that presented estrogen dose results stratified by low or high progestin dose, odds ratios for groups with identical estrogen doses were combined across progestin arms using an inverse weighted meta-analysis. In order to compare high- to low-dose estrogen, we included those studies that had odds ratios for each with "never use" as a reference category and divided the high-dose odds ratio by the low-dose odds ratio. This has the effect of canceling out the never-use category. All analyses were made using a random-effects model.

Progestin

Studies were included in the meta-analysis if they reported the effect of low- and/or high-dose progestin on ovarian cancer incidence and presented an established reference for determination of progestin potency. For studies that stratified these results based on low or high estrogen dose, odds ratios for identical progestin dose groups were combined across estrogen arms using an inverse weighted meta-analysis. In order to compare high- to low-dose progestin, we included those studies that had odds ratios for each with "never use" as a reference category and divided the high-dose odds ratio by the low-dose odds ratio. This has the effect of canceling out the never-use category. All analyses were made using a random-effects model.

Special Populations

BRCA Mutation Carriers

Studies were included in the meta-analyses of BRCA mutation carriers if they reported the effect of OCs on ovarian cancer risk comparing mutation carriers with ovarian cancer to unaffected mutation carriers. The analyses were restricted to these study populations because they address the most relevant clinical question: If a woman tests positive for mutations in BRCA1 or BRCA2, can she reduce her risk for ovarian cancer by taking OCs? Studies that compare cases who are mutation carriers with controls who are not mutation carriers do not provide a direct answer to the clinical question because the comparison involves both a genetic factor (BRCA1 or BRCA2 mutation) and an environmental factor (OC use)—this study design does not allow us to sort out the relative contributions of these factors to ovarian cancer risk.

Separate meta-analyses were performed for studies reporting results for BRCA1 mutation carriers, BRCA2 mutation carriers, and BRCA1 and BRCA2 mutation carriers combined.

Family History of Ovarian Cancer

Studies were considered eligible for inclusion if they reported the effect of OCs on ovarian cancer risk stratified by family history.

Parity/Gravidity

Studies were included in the meta-analysis if they reported the effect of OCs on ovarian cancer risk stratified by parity or gravidity. We did not distinguish between parity and gravidity in our analyses. For studies that split parity into multiple categories (i.e., 0, 1, 2, 3+), the results were combined across parity categories using an inverse weighted meta-analysis, and these were labeled parity 1+. To compare parity 0 to parity 1+, we computed the ratio of the parity 0 odds ratio and the parity 1 odds ratio for each study. This has the effect of canceling out the never-use category, which is the reference. All analyses were performed using a random-effects model.

Results

This section presents results of our detailed analysis of the relationship between OCs and ovarian cancer incidence and ovarian cancer mortality.

OC Use and Ovarian Cancer Incidence

We identified 55 studies that evaluated the association between OC use and the incidence of ovarian cancer.[21,23,24,29,37,81-162] In Table 5, we list the studies that reported odds ratios for ever versus never OC use. Of these studies, 28 were case-control studies, 10 were cohort studies, and the remaining 4 were pooled analyses. Of the case-control and cohort studies, 17 studies were rated good quality, 20 fair quality, and 5 poor quality. (As described in the Methods, studies represented by multiple articles and abstracted into more than one dataset may be counted in more than one quality category. Quality ratings specific to each of these datasets are provided in Table 5). Note that none of the pooled analyses met criteria for inclusion in the meta-analyses examining OC use and ovarian cancer incidence.

Table 5. Study characteristics and association between OC use and ovarian cancer incidence

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
			Case-Control				
Gwinn, 1990[96]	**Women <55 yr enrolled in the Cancer and Steroid Hormone Study** Cases: 436 epithelial ovarian cancers including borderline tumors Controls: 3833 population-based controls	0.566	0.48 to 0.69	Age, parity, breastfeeding	U.S.	Good	8
Parazzini, 1991[128]	**Italian women <60 yr** Cases: 505 epithelial ovarian cancers Controls: 1375 hospital-based controls *Parity 0* Cases: 137 epithelial ovarian cancers Controls: 273 hospital-based controls *Parity 1-2* Cases: 266 epithelial ovarian cancers Controls: 795 hospital-based controls *Parity 3+* Cases: 102 epithelial ovarian cancers Controls: 307 hospital-based controls	0.7 0.6 0.5 0.8	0.5 to 1.0 0.3 to 1.3 0.3 to 0.9 0.3 to 1.7	Age, parity, menopausal status, age at menarche, education, marital status, lifelong menstrual pattern, age at menopause	Europe	Good	3[127]
Parazzini, 1991[129]	**Italian women <65 yr with borderline tumors** Cases: 91 borderline ovarian tumors Controls: 273 hospital-based controls	0.3	0.2 to 0.6	Age, parity, education, age at menopause	Europe	Good	8

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Thomas, 1991[150]	**WHO Collaborative Study of Neoplasia and Steroid Contraceptives** Cases: 368 epithelial ovarian cancers Controls: 2397 hospital-based controls	0.75	0.56 to 1.01	Age, parity, hospital, year of interview	Europe, Asia, Africa, Australia/ NZ, Israel, Mexico	Fair	8
	Borderline tumors Cases and controls: NR	0.81	0.45 to 1.47				
	Invasive ovarian cancer Cases and controls: NR	0.72	0.51 to 1.02				
	Nulliparous women Cases and controls: NR	0.16	0.05 to 0.54				
	Parous women Cases and controls: NR	0.85	0.63 to 1.16				
Badawy, 1992[82]	**Saudi Arabian women** Cases: 52 ovarian cancer cases Controls: 52 population-based controls	0.4	0.2 to 0.8	None	Saudi Arabia	Poor	8
Poly-chronopoulou, 1993[131]	**Greek women age <75 yr** Cases: 189 malignant epithelial ovarian tumors Controls: 200 population-based controls	0.8	0.17 to 3.67	Age, parity, menopausal status, age at menarche, smoking, education, weight, age at menopause, coffee, alcohol, age at first birth	Europe	Poor	8
Rosenberg, 1994[137]	**Women age <65 yr** Cases: 441 invasive ovarian cancer cases Controls: 2065 hospital-based controls	0.8	0.6 to 1.0	Age, race, parity, family history, hysterectomy, tubal ligation, removal of one ovary, geographic area, interview year	U.S.	Fair	8

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Narod, 1998[122]	**International consortium of women with BRCA1/2 mutations** Cases: 207 invasive epithelial ovarian cancer Controls: 161 sisters of women with mutations and ovarian cancers Cases: 207 invasive epithelial ovarian cancer Controls: 53 sisters of women with mutations and ovarian cancers who are also known mutation carriers without a personal history of ovarian cancer	0.5 0.4	0.3 to 0.8 0.2 to 0.7	Age, parity, age at first birth, geographic area of residence	U.S., Canada, UK, Europe	Fair	2
Wittenberg, 1999[161]	*Mucinous ovarian cancers* Cases: 43 mucinous epithelial ovarian cancers Controls: 426 population-based controls *Nonmucinous ovarian cancers* Cases: 279 nonmucinous epithelial ovarian cancers Controls: 426 population-based controls	0.9 0.8	0.4 to 2.1 0.6 to 1.3	Age, parity, duration of OC use	U.S.	Fair	8
Beard, 2000[83]	**Olmstead County women** Cases: 103 women with invasive epithelial ovarian cancers Controls: 103 population-based controls	1.1	0.6 to 2.3	No adjustment, but matched by age	U.S.	Fair	1
Greggi, 2000[93]	**Italian women** Cases: 440 epithelial ovarian cancer Controls: 868 hospital-based controls	0.4	0.3 to 0.6	Age, parity, family history, breastfeeding , education, OC use, age at first birth, breast feeding, duration of use	Europe	Good	1
Ness, 2000[125]	**SHARE Study participants age <70 yr** Cases: 767 Controls: 1367	0.6	0.5 to 0.8	Age, race, family history, number of pregnancies	U.S.	Good	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Case-Control (continued)							
Parazzini, 2000[127]	**Italian women** Cases: 971 epithelial ovarian cancer cases Controls: 2758 hospital-based controls	1.2	1.0 to 1.7	Age, parity, calendar year of interview, age at menopause, family history of breast or ovarian cancer, green vegetable consumption, fat-intake score	Europe	Good	1
Sanderson, 2000[143]	**White women age <70 yr** Cases: 276 epithelial ovarian cancer cases Controls: 388 population-based controls	0.8	0.5 to 1.1	Age, parity	U.S.	Good	1
Siskind, 2000[145]	**Australian women** *Nonmucinous ovarian cancers* Cases: 677 Controls: 853 *Mucinous ovarian cancers* Cases: 114 Controls: 853	0.64 0.61	0.48 to 0.85 0.36 to 1.04	Age, parity, BMI, family history, breastfeeding , age squared, alcohol, hysterectomy, tubal, infertility, number of lifetime ovulation	Australia/ NZ	Good	1[144]
Chiaffarino, 2001[87]	**Italian women** Cases: 1031 ovarian cancer cases Controls: 2411 hospital-based controls	0.9	0.7 to 1.2	Age, parity, family history, center, education	Europe	Fair	1
Riman, 2001[133]	**Swedish women with borderline ovarian tumors** Cases: 193 borderline cases Controls: 3899 population-based controls	1.23	0.86 to 1.76	Age, parity, BMI, age menopause, HRT	Europe	Fair	1
Royar, 2001[141]	**German women** Cases: 282 invasive ovarian cancer cases Controls: 533 population-based controls	0.48	0.33 to 0.68	Parity, Family History, Breastfeeding , tubal ligation, hysterectomy	Europe	Fair	1
Riman, 2002[134]	**Swedish women with epithelial ovarian cancer** Cases: 655 ovarian cancer cases Controls: 3899 population-based controls	0.73	0.59 to 0.90	Age, parity, BMI, age at menopause, HRT	Europe	Fair	1

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Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Tung, 2003[152]	**Residents of Hawaii or Los Angeles County** Cases: 603 ovarian cancer cases Controls: 607 population-based controls	0.6	0.4 to 0.8	Age, race, parity, study site, education, tubal ligation	U.S.	Good	3[114]
McGuire, 2004[115]	**Women in Northern California** *Women with BRCA1 mutations* Cases: 36 epithelial ovarian cancer cases Controls: 568 population-based controls *Women without BRCA1 mutations* Cases: 381 epithelial ovarian cancer cases Controls: 568 population-based controls	0.54 0.55	0.26 to 1.13 0.41 to 0.73	Age, race, parity	U.S.	Good	1
Whittemore, 2004[159]	**International database of BRCA1/2 carriers** Cases: 147 BRCA carriers with epithelial ovarian cancer Controls: 304 BRCA carriers without epithelial ovarian cancer	0.85	0.53 to 1.4	Age, parity, center	U.S., Canada, UK, Australia/ NZ	Fair	2
Quirk, 2004[132]	**Women from Roswell Park Cancer Institute, New York** Cases: 418 invasive ovarian cancer cases Controls: 836 hospital-based controls	1.22	0.88 to 1.68	Age, parity, family history, history of tubal ligation, noncontraceptive estrogen use	U.S.	Poor	1
Greer, 2005[91]	**Women from the Study of Health and Reproduction (SHARE)** Cases: 405 Controls: 592 *Compared never users with nonandrogenic OC users* Cases: 381 Controls: 761 *Compared never users with both androgenic and nonandrogenic OC users* Cases: 364 Controls: 529	0.52 0.59 0.29	0.35 to 0.76 0.45 to 0.78 0.17 to 0.48	Age, parity, family history, BTL	U.S.	Fair	3[125]
Gronwald, 2006[94]	**Polish BRCA1 carriers** Cases: 150 ovarian cancer cases Controls: 150 population-based controls	0.4	0.2 to 1.0	None	Europe	Fair	2

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Huusom, 2006[107]	**Women participating in the MALOVA study** Cases: 202 ovarian borderline cases Controls: 1564 population-based controls	0.81	0.56 to 1.16	Age, parity, smoking, breastfeeding , age at first birth, duration of contraception use, intake of milk	Denmark	Fair	1
Lurie, 2007[113]	**Residents of Hawaii or Los Angeles County** Cases: 745 epithelial ovarian cancer cases Controls: 943 population-based controls	0.51	0.26 to 0.98	Unclear	U.S.	Good	3[114]
McLaughlin, 2007[116]	**International consortium of women with BRCA1** and/or BRCA2 mutations Cases: 799 mutation carriers with ovarian cancer Controls: 2424 mutation carriers without ovarian cancer *BRCA1 carriers only* Cases: 670 mutation carriers with ovarian cancer Controls: 2043 mutation carriers without ovarian cancer *BRCA2 carriers only* Cases: 128 mutation carriers with ovarian cancer Controls: 380 mutation carriers without ovarian cancer	0.53 0.56 0.39	0.43 to 0.66 0.45 to 0.71 0.23 to 0.66	Parity, breastfeeding , tubal ligation, ethnicity	U.S., Canada, UK, Europe, Asia	Good	2

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Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Soegaard, 2007[146]	**Women participating in the MALOVA study** Cases: 554 ovarian cancer cases Controls: 1564 population-based controls	0.67	0.53 to 0.85	Age, parity	Denmark	Good	1
	Mucinous ovarian cancers Cases: 50 ovarian cancer cases Controls: 1564 population-based controls	0.49	0.25 to 0.97				
	Serous ovarian cancers Cases: 343 ovarian cancer cases Controls: 1564 population-based controls	0.7	0.52 to 0.94				
	Endometrioid ovarian cancers Cases: 75 ovarian cancer cases Controls: 1564 population-based controls	0.76	0.42 to 1.35				
	"Other" histologic types of ovarian cancer Cases: 86 ovarian cancer cases Controls: 1564 population-based controls	0.62	0.36 to 1.06				
Lurie, 2008[114]	**Residents of Hawaii or Los Angeles County** Cases: 813 epithelial ovarian cancer cases Controls: 993 population-based controls	0.59	0.42 to 0.84	Age, race, menopausal status, family history, education, gravidity, age at last pregnancy, tubal ligation, OC potency, hysterectomy, age at menopause, use of menopausal hormones	U.S.	Good	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Moorman, 2008[121]	**Women in the North Carolina Ovarian Cancer Study** *Premenopausal* Cases: 314 epithelial ovarian cancer cases Controls: 360 population-based controls *Postmenopausal* Cases: 582 epithelial ovarian cancer cases Controls: 607 population-based controls	0.5 0.8	0.3 to 0.8 0.6 to 1.1	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	U.S.	Good	1
Boyce, 2009[84]	*Granulosa cell tumors* Cases: 72 GCT cases Controls: 1578 population-based controls *Granulosa cell tumors vs. epithelial ovarian cancer* Cases: 72 GCT cases Controls: 1511 epithelial ovarian cancer cases	0.32 0.6	0.17 to 0.63 0.32 to 1.14	Age, race	U.S.	Fair	4
Ness, 2011[123]	**HOPE study participants** Cases: 869 women with invasive and borderline ovarian cancer Controls: 1779 population-based controls	0.67	0.55 to 0.81	Age, race, family history, gravidity, infertility, ever use of IUDs or barrier contraceptives, tubal ligation, and vasectomy	U.S.	Good	1
Urban, 2012[155]	**Black South African women aged 18–79 yr** Cases: 182 ovarian cancer cases Controls: 1492 women with cancers with no known relationship to oral or injectable contraception Recruitment period: 1995–2006	0.88	0.52 to 1.50	Age, parity, smoking, year of diagnosis, education, alcohol consumption, number of sexual partners, urban/rural residence, province of birth	South Africa	Good	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Wilailak, 2012[160]	**Thai women** Cases: 330 epithelial ovarian cancer cases Controls: 982 hospital-based controls	0.71	0.51 to 0.98	Parity, family history, breastfeeding, depot medroxy-progesterone acetate use	Thailand	Fair	1
			Cohort				
Hankinson, 1995[98]	**Nurses' Health Study** Exposed: 592,056 person-years OC exposed Unexposed: 599,301 person-years OC unexposed	1.08	0.83 to 1.43	Age, parity, menopausal status, age at menarche, smoking, BTL, Quetelet's Index	U.S.	Fair	8
Vessey, 1995[157]	**Oxford Family Planning Association Contraceptive Study** Exposed: 3520 women >8 years OC exposed Unexposed: 5881 women OC unexposed	0.4	0.2 to 0.8	Age, parity	UK	Poor	3[156]
Kumle, 2004[110]	**Norwegian-Swedish Women's Lifestyle and Health cohort** Exposed: 75,533 women OC exposed Unexposed: 28,019 women OC unexposed *Invasive ovarian cancers* *Borderline ovarian tumors*	0.6 0.6 0.7	0.5 to 0.8 0.4 to 0.8 0.5 to 1.2	Age, parity, menopausal status, HRT, country	Europe	Fair	1
Vessey, 2006[156]	**Oxford Family Planning Association Contraceptive Study** Exposed: 301,000 person-years OC exposed Unexposed: 187,000 person-years OC unexposed	0.5	0.3 to 0.7	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Hannaford, 2007[37]	**Royal College of General Practitioners Oral Contraception Study** *Main dataset* Exposed: 744,000 person-years of observation Unexposed: 339,000 person-years of observation *General practitioner dataset* Exposed: 744,000 person-years of observation Unexposed: 339,000 person-years of observation	0.54 0.51	0.40 to 1.71 0.33 to 0.78	Age, parity, smoking, social status	UK	Fair	1
Antoniou, 2009[81]	**International BRCA1/2 Carrier Cohort Study** *BRCA1/2 mutation carriers* Exposed: 2415 women OC exposed Unexposed: 766 women OC unexposed *BRCA1 mutation carriers* Exposed: 1655 women OC exposed Unexposed: 512 women OC unexposed *BRCA2 mutation carriers* Exposed: 760 women OC exposed Unexposed: 245 women OC unexposed	0.55 0.52 1.04	0.40 to 0.76 0.37 to 0.73 0.42 to 2.54	Parity	Canada, UK, Europe	Fair	2
Dorjgochoo, 2009[88]	**Shanghai Women's Health Study** Exposed: 12,957 women OC exposed Unexposed:15,557 women OC unexposed	1.19	0.66 to 1.84	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods	Asia	Fair	1

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort (continued)							
Rosenblatt, 2009[138]	**Cohort of female textile workers in Shanghai** Exposed: 352,695 person-years OC exposed Unexposed: 2,057,377 person-years OC unexposed	1.17	0.86 to 1.60	Age, parity, injectable contraceptive use	Asia	Poor	1
Braem, 2010[85]	**Netherlands Cohort Study on Diet and Cancer** Exposed: 8668 person-years OC exposed Unexposed: 25,916 person-years OC unexposed	0.71	0.52 to 0.97	Age, parity	UK, not multi-center	Fair	5
Tsilidis, 2011[151]	**EPIC Cohort** Exposed: 192,836 women OC exposed Unexposed: 132,923 women OC unexposed	0.86	0.73 to 1.00	Age, parity, menopausal status, BMI, smoking, center, unilateral oophorectomy, hysterectomy, menopausal hormones, age at menarche	Europe	Good	1
Yang, 2012[162]	**NIH-AARP Diet and Health Study** Exposed: 67,870 women OC exposed Unexposed: 100,304 women OC unexposed	0.74	0.63 to 0.87	Age, parity, menopausal hormone therapy	U.S.	Good	1
Pooled							
Franceschi, 1991[24]	Cases: 971 women with epithelial ovarian cancer Controls: 2258 hospital controls	0.6	0.4 to 0.8	Study, age, marital status, socioeconomic status, parity, menopause, contraceptive habits	Europe	Fair	7
Harris, 1992[101]	**Collaborative Ovarian Cancer Group** Cases: 327 white women with ovarian borderline tumors Controls: 4144 white controls	0.80	0.59 to 1.1	Study, age, parity	U.S.	Good	7

Table 5. Study characteristics and association between OC use and ovarian cancer incidence (continued)

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Pooled (continued)							
Horn-Ross, 1992[106]	**Collaborative Ovarian Cancer Group** *Germ cell tumors* Cases: 38 Controls: 1142 general population controls *Sex cord-stromal tumors* Cases: 45 Controls: 2617 general population controls	2.0 0.37	0.77 to 5.1 0.16 to 0.83	Study, age, year of birth	U.S.	Fair	4, 7
Bosetti, 2002[23]	Cases: 2,768 women with epithelial ovarian cancer Controls: 6,274 hospital controls	0.66	0.56 to 0.79	Study, age, year, socioeconomic status, parity, menopause, age at menopause	Europe	Fair	6
Beral, 2008[21]	Cases: 23,257 women with malignant ovarian tumors Controls: 87,303 women without malignant ovarian tumors	0.73	0.70 to 0.76	Study, age, parity, hysterectomy	21 countries	Good	6

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; GCT = granulosa cell tumor; HRT = hormone replacement therapy; IUD = Intrauterine device; OC = oral contraceptive; OR = odds ratio; NR = not reported; NZ = New Zealand; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 1 = Included in this meta-analysis; 2 = Excluded due to odds ratios reported for BRCA mutation carriers only; 3 = Excluded due to odds ratios for this population reported by another included article (primary abstraction ID given); 4 = Excluded due to epithelial ovarian cancers not included; 5 = Excluded due to case-cohort study reported hazard ratio only; 6 = Excluded pooled study due to inclusion of component studies; 7 = Excluded pooled study due to >50% of component studies published prior to 1990; 8 = Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

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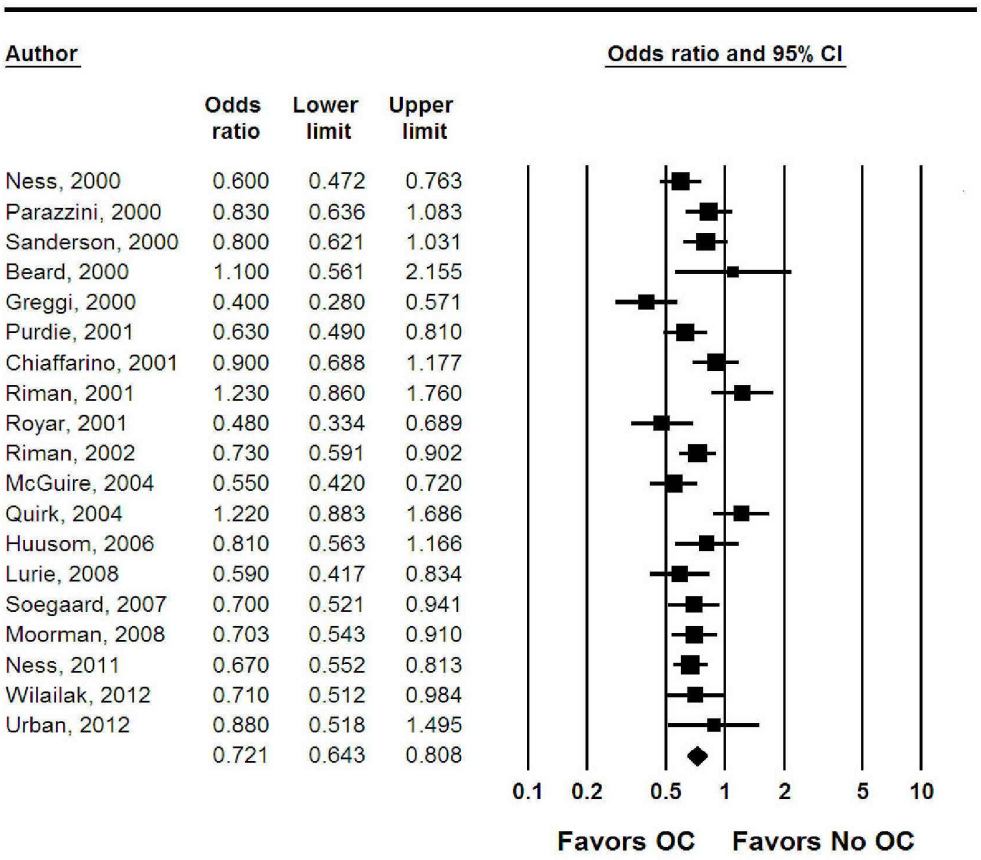
Ever Versus Never OC Use

Seventeen case-control studies representing 10,031 cases and 21,025 controls[83,87,93,107,114,115,121,123,125,127,132-134,141,143-146,155,160] and including two instances of paired articles from the same studies with distinct cases[107,133,134,146] were included in this meta-analysis examining the effect of ever versus never OC use on ovarian cancer incidence. Of these studies, 11 were rated good quality, 6 fair quality, and 1 poor quality. Note that the articles from the MALOVA study are represented in two different quality categories based on varying characteristics of the two publications. Abstracted data not included in this analysis are specified (with rationale) in Table 5. Reasons for exclusion from the analysis included reporting ever versus never data from the same study as another article already included in the analysis; reporting only on BRCA mutation carriers; and including only women with nonepithelial ovarian cancers. Figure 10 shows that the odds ratio for the meta-analysis of ever versus never use of OCs was 0.72 (95% CI, 0.64 to 0.81), which demonstrates an almost 28-percent reduction in ovarian cancer risk in women who have ever used OCs.

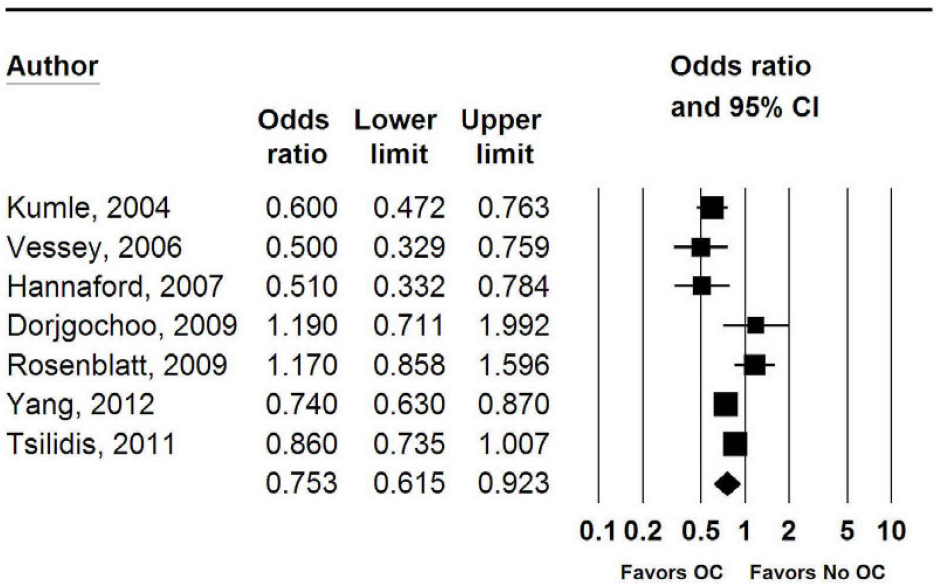
Figure 10. Forest plot for ever versus never OC use (case-control studies, ovarian cancer incidence)



CI = confidence interval; OC = oral contraceptive

Seven cohort studies[37,88,110,138,151,156,162] were included in this meta-analysis. There was a total of 625,999 participants in four of these studies[88,110,151,162] and a total of 3,981,072 person-years of followup in the other three.[37,138,156] Of these studies, three were rated good quality, three fair quality, and one poor quality. Abstracted data not included in this analysis are specified (with rationale) in Table 5. Reasons for exclusion from this analysis included reporting only on BRCA mutation carriers; reporting ever versus never data from the same study as another article already included in the analysis; and for one case-cohort study, reporting hazard ratios rather than odds ratios. Figure 11 shows that the odds ratio for the meta-analysis of ever versus never use of OCs was 0.75 (95% CI, 0.62 to 0.92).

Figure 11. Forest plot for ever versus never OC use (cohort studies, ovarian cancer incidence)



CI = confidence interval; OC = oral contraceptive

A combined meta-analysis of all 24 case-control and cohort studies resulted in an odds ratio for ever versus never use of 0.73 (95% CI, 0.66 to 0.81). Both groups of studies showed heterogeneity due to heterogeneous populations and varying durations of followup.

Sensitivity Analyses

Analyses were repeated excluding the studies rated as poor quality (1 case-control and 1 cohort). These exclusions had a minor effect on the odds ratio estimates. Estimates were 0.70 (95% CI, 0.63 to 0.78) for the case-control studies; 0.70 (CI, 0.58 to 0.85) for the cohort studies; and 0.70 (CI, 0.64 to 0.77) for all studies combined. We also repeated our analyses of the case-control studies excluding those without patients from the United States (9 studies). The meta-analysis of the remaining eight case-control studies revealed an odds ratio for ever OC use of 0.72 (CI, 0.61 to 0.85). A similar analysis was not performed for the cohort studies because only one of the seven studies was conducted in the United States.

Additional analyses were done including studies published from 1990 forward. Estimates were 0.70 (CI, 0.63 to 0.77) for the 26 case-control studies, 0.79 (CI, 0.65 to 0.96) for the 8 cohort studies and 0.72 (CI, 0.66 to 0.79) for a combined analysis of the case-control and cohort studies.

Pooled Analyses

Two pooled analyses that reported on ever versus never OC use but did not meet inclusion criteria for the meta-analysis are of particular note. One of these[23] included only epithelial ovarian cancers as cases and reported odds ratios for ever versus never use of 0.66 (95% CI, 0.56 to 0.79). The other[21] reported the largest pooled analysis of 45 studies (47 referenced publications) with 23,257 cases of epithelial or nonepithelial ovarian cancer and 87,303 controls—with a combined odds ratio of 0.73 (CI, 0.70 to 0.76). Our systematic review included 13 of the 47 studies referenced by Beral et al.[21] Of the remaining 34 studies, 16 were not included due to publication prior to 2000; 16 were not identified by our literature search, and manual review of these confirmed that they were not relevant to our question of interest; and 2 were identified by the literature search but excluded at the abstract screening stage.

Temporal Relationships

Duration of OC Use

Fifteen studies[37,87,109,110,114,117,118,125,133,134,138,141,145,152,154,160,162] were included in this meta-analysis examining the effect of duration of OC use on ovarian cancer incidence. Of these, 10 were case-control studies representing 6901 cases and 15,999 controls. Five were cohort studies, with 524,463 participants in 3 of the studies and 3,493,072 person-years in the other 2 studies. Seven studies were rated good quality, 7 fair quality, and 1 poor quality. Reasons for exclusion from this meta-analysis included reporting fewer than 3 duration categories; reporting odds ratios only for specific subpopulations of women; lacking a “never use” reference group; reporting duration data from the same study as another article already included in the analysis; and reporting duration odds ratios for only the year of OC use (Table 6).

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control							
Harlow, 1991[100]	Cases: 194 Controls: 193	Used OC for <3 mo or never (reference) 3 to 12 mo 13 to 48 mo >48 mo	1.0 1.5 0.7 0.5	NA (reference) 0.8 to 3.1 0.3 to 1.4 0.2 to 0.9	Age, parity, religion		3
Parazzini, 1991[128]	Cases: 505 Controls: 1375	<2 yr ≥2 yr	0.9 0.5	0.5 to .5 0.3 to 0.9	Age, parity, menopausal status, age at menarche, education, marital status, lifelong menstrual pattern, age at menopause		2
Parazzini, 1991[129]	Cases: 91 Controls: 273	<24 mo ≥24 mo	0.3 0.2	0.1 to 0.4 0.1 to 0.6	Age, parity, education, age at menopause		2
Thomas, 1991[150]	Cases: 368 Controls: 2397	1 to 11 mo 12 to 59 mo 60+ mo	0.86 0.69 0.50	0.58 to 1.28 0.45 to 1.10 0.26 to 0.98	Age, menopausal status, hospital, year of interview		2
Badawy, 1992[82]	Cases: 52 Controls: 52	<5 yr 5+ yr	0.9 0.2	0.3 to 2.5 0.1 to 0.5	Crude		2
Chen, 1992[86]	Cases: 112 Controls: 224	<12 mo 12 to 35 mo 36+ mo	0.7 1.4 1.1	Reference 0.3 to 1.8 0.5 to 3.4 0.4 to 2.9	Parity, education		7
Gross, 1992[95]	Cases: 225 Controls: 2252	3 to 11 mo 12 to 24 mo 25 to 36 37 to 60 ≥61	0.6 0.6 0.7 0.7 0.3		Age, parity	Cases and controls with no family history of ovarian cancer	4
	Cases: 31 Controls: 99	3 to 11 mo 12 to 24 mo 25 to 36 mo 37 to 60 mo ≥61 mo	3.1 1.7 1.5 1.1 0.3		Age, parity	Women with a family history of ovarian cancer	4

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Rosenblatt, 1992[140]	Cases: 393 Controls: 2561	High dose 1 to 6 mo High dose 7 to 18 mo High dose 19 to 60 mo High dose 61+ mo Low dose 1 to 6 mo Low dose 7 to 18 mo Low dose 19 to 60 mo Low dose 61+ mo	0.60 1.07 0.48 0.49 0.45 1.36 1.47 0.75	0.28 to 1.28 0.50 to 2.29 0.20 to 1.18 0.17 to 1.43 0.18 to 1.10 0.59 to 3.10 0.68 to 3.18 0.26 to 2.19	Age, parity, center, year of diagnosis		4
Tavani, 1993[148]	Cases: 194 Controls: 710	2 yr or less 2 to <5 yr 5+ yr	0.9 1.1 0.3	0.5 to 1.4 0.5 to 2.4 0.1 to 0.7	Age, parity, family history, education, abortions, OC use	Only women <45 yr	7
Rosenberg, 1994[137]	Cases: 441 Controls: 2065	1 to 5 mo 6 to 11 mo 1 yr 2 yr 3 to 4 yr 5 to 9 yr ≥10 yr	1.1 0.9 1.3 1.2 0.5 0.7 0.5	0.7 to 1.7 0.5 to 1.7 0.8 to 2.0 0.7 to 2.0 0.3 to 1.1 0.4 to 1.1 0.2 to 0.9	Age, race, parity, family history, hysterectomy, removal of one ovary, geographic area, interview year	Formulation data refers only to use >3 yr	7
Risch, 1996[136]	Cases: 367 Controls: 564	OR per yr OC use	0.89	0.84 to 0.94	Age, parity, family history, breastfeeding, duration of OC use, BTL, HRT, hysterectomy	Invasive serous ovarian cancers	5
	Cases: 83 Controls: 564	OR per yr OC use	0.95	0.9 to 1.01	Age, parity, family history, breastfeeding, duration of OC use, BTL, HRT, hysterectomy	Borderline tumors	5
	Cases: 40 Controls: 564	OR per yr OC use	0.97	0.89 to 1.05	Age, parity, family history, breastfeeding, duration of OC use, tubal ligation, HRT, hysterectomy	Mucinous invasive cancers	5

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Risch, 1996[136] (continued)	Cases: 42 Controls: 564	OR per yr OC use	0.86	0.77 to 0.96	Age, parity, family history, breastfeeding, duration OC use, HRT, BTL, hysterectomy	Borderline serous tumors	5
	Cases: 40 Controls: 564	OR per yr OC use	1.00	0.93 to 1.07	Age, parity, family history, breastfeeding, duration OC use, HRT, BTL, hysterectomy	Borderline mucinous tumors	5
	Cases: 254 Controls: 564	OR per yr OC use	0.88	0.84 to 0.93	Age, parity, family history, breastfeeding, duration OC use, HRT, BTL, hysterectomy	All serous tumors both borderline and invasive	5
	Cases: 367 Controls: 564	OR per yr of OC use	0.9	0.86 to 0.94	Age, parity, family history, breastfeeding, BTL, HRT, hysterectomy, duration of OC use	Invasive ovarian cancers	5
Godard, 1998[89]	Cases: 153 Controls: 152	0 to 1 yr 1 to 5 yr 6 to 10 yr 11 to 25 yr Per yr of use	1.0 0.77 0.49 0.33 0.89	Reference 0.44 to 1.36 0.27 to 0.91 0.13 to 0.82	Crude		3

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Narod, 1998[122]	Cases: 207 Controls: 53	<3 yr 3 to <6 yr ≥6 yr	0.4 0.4 0.3	0.3 to 0.9 0.1 to 1.0 0.1 to 0.7	Age, parity, age at first birth, geographic area of residence	Ovarian cancer cases with BRCA1 or BRCA2 mutations, controls are sisters of cases (53 of 161 controls had BRCA1 or BRCA2 mutations).Cases compared with controls with BRCA1/2 mutations	4
	Cases: 207 Controls: 161	<3 yr 3 to <6 yr ≥6 yr	0.8 0.4 0.4	0.4 to 1.4 0.2 to 0.9 0.2 to 0.7	Age, parity, age at first birth, geographic area of residence	Cases with BRCA1 or BRCA2 mutations, controls are sisters of cases (53 of 161 had BRCA1 or BRCA2 mutations)	4
Salazar-Martinez, 1999[142]	Cases: 84 Controls: 668	1 to 12 mo 13+ mo	0.56 0.36	0.22 to 1.3 0.15 to 0.83	Age, parity, BMI, smoking, breastfeeding , diabetes, hypertension, physical activity, menopausal status		2

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Wittenberg, 1999[161]	Cases: 322 Controls: 426	<5 yr 5+ yr	1.0 0.6	0.7 to 1.6 0.4 to 1.0	Age, parity	Nonmucinous cases	2
	Cases: 322 Controls: 426	<5 yr 5+ yr	1.2 0.4	0.5 to 3.0 0.1 to 1.4	Age, parity	Mucinous ovarian cases	2
Greggi, 2000[93]	Cases: 440 Controls: 868	< 24 mo ≥24 mo	0.5 0.3	0.3 to 0.9 0.2 to 0.5	Age, parity, family history, breastfeeding, education, OC use, age at first birth, breast feeding, OC use		2
Ness, 2000[125]	Cases: 616 Controls: 1367	< 1 yr 1 to 4 yr 5 to 9 yr ≥10 yr	0.7 0.7 0.7 0.4	0.5 to 1.0 0.5 to 0.9 0.5 to 0.9 0.2 to 0.6	Age, race, family history, number of pregnancies	Invasive ovarian cancer (N=616)	1
	Cases: 767 Controls: 1367	< 1 yr 1 to 4 yr 5 to 9 yr ≥10 yr	0.7 0.7 0.6 0.3	0.6 to 1.0 0.5 to 0.9 0.5 to 0.9 0.2 to 0.5	Age, race, family history, number of pregnancies	All cases combined	1
	Cases: 151 Controls: 1367	< 1 yr 1 to 4 yr 5 to 9 yr ≥10 yr	1.0 0.8 0.7 0.3	0.6 to 1.7 0.5 to 1.3 0.4 to 1.2 0.1 to 0.7	Age, race, family history, number of pregnancies	Borderline ovarian cancer (N=151)	1
Sanderson, 2000[143]	Cases: 276 Controls: 388	<5 yr >5 yr	1.0 0.6	0.6 to 1.5 0.3 to 0.9	Age, parity		2

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Siskind, 2000[145]	Cases: 794 Controls: 853	1 to 12 mo 13 to 60 mo 61 to 120 mo 120 to 180 mo >180 mo 1 to 12 mo prior to first pregnancy 13 to 36 mo prior to first pregnancy 36 to 60 mo prior to first pregnancy >60 mo prior to first pregnancy	0.57 0.73 0.50 0.35 0.25 1.01 0.97 0.89 0.54	0.40 to 0.82 0.52 to 1.03 0.34 to 0.73 0.21 to 0.56 0.13 to 0.49 0.57 to 1.80 0.58 to 1.63 0.47 to 1.68 0.26 to 1.11	Parity, smoking, ovulatory life, tubal ligation, and hysterectomy		1
	Cases: 114 Controls: 853	OR per year of OC use	0.92	0.88 to 0.97	Age, parity, BMI, family history, smoking, breastfeeding , alcohol, BTL, hysterectomy, infertility, number of lifetime ovulations	Mucinous ovarian cancers	1
	Cases: 677 Controls: 853	OR per year of OC use	0.93	0.90 to 0.96	Age, parity, BMI, smoking, age squared, alcohol, hysterectomy, tubal, infertility, number of lifetime ovulation	Nonmucinous ovarian cancer	1
Chiaffarino, 2001[87]	Cases: 1031 Controls: 2411	<25 mo 25 to 59 mo ≥60 mo	1.0 1.3 0.5	0.7 to 1.4 0.7 to 2.2 0.3 to 0.9	Age, parity, family history, center, education		1

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Modan, 2001[118]	Cases: 240 Controls: 2257	0.1 to 1.9 yr 2.0 to 4.9 yr ≥5.0 yr	1.14 0.77 1.07	0.67 to 1.94 0.41 to 1.44 0.63 to 1.83	Age, parity, family history, personal history of breast cancer, history of gynecologic surgery, ethnicity	Israeli population; cases with BRCA1 or 2 mutations (N=240)	1
	Cases: 832 Controls: 2257	0.1 to 1.9 yr 2.0 to 4.9 yr ≥5.0 yr	1.15 0.77 0.69	0.84 to 1.57 0.53 to 1.12 0.48 to 0.98	Age, parity, family history, personal history of breast cancer, history of gynecologic surgery, ethnicity	Israeli population; high prevalence of BRCA mutation carriers	1
	Cases: 592 Controls: 2257	0.1 to 1.9 yr 2.0 to 4.9 yr ≥5.0 yr	1.13 0.74 0.53	0.79 to 1.62 0.48 to 1.16 0.34 to 0.84	Age, parity, family history, personal history of breast cancer, history of gynecologic surgery, ethnicity	Israeli population; cases without BRCA mutations (N=592)	1

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Modugno, 2001[119]	Cases: 616 Controls: 1367	Per one year of use	0.94	0.92 to 0.97	Age, race, parity, family history, breastfeeding , noncontraceptive estrogen use, tubal ligation, hysterectomy, family history of breast cancer	Invasive ovarian cancer (N=616)	5
	Cases: 151 Controls: 1367	Per one year of use	0.92	0.85 to 0.98	Age, race, parity, family history, breastfeeding , noncontraceptive estrogen use, tubal ligation, hysterectomy, family history of breast cancer	Borderline ovarian cancer (N=151)	5
	Cases: 767 Controls: 1367	Per year of use	0.94	0.91 to 0.96	Age, race, parity, family history, breastfeeding , noncontraceptive estrogen, tubal ligation, hysterectomy, family history of breast cancer		5

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Ness, 2001[126]	Cases: 727 Controls: 1359	OCs for contraception ≤4 yr OCs for contraception 5 to 9 yr OCs for contraception ≥10 yr OCs for noncontraception ≤4 yr OCs for noncontraception 5 to 9 yr OCs for noncontraception ≥10 yr OCs for both ≤4 yr OCs for both 5 to 9 yr OCs for both ≥10 yr	0.6 0.5 0.3 0.7 NR NR 0.7 0.8 0.2	0.5 to 0.8 0.4 to 0.8 0.2 to 0.6 0.4 to 1.0 0.5 to 1.1 0.5 to 1.4 0.5 to 1.4 (Not plausible for reported OR)	Age, race, family history, pregnancies		4
Riman, 2001[133]	Cases: 193 Controls: 3899	<2 y 2 to 4 y 5 to 9 y ≥10 y	0.96 1.34 1.29 1.16	0.55 to 1.66 0.73 to 2.43 0.68 to 2.43 0.61 to 2.18	Age, parity, BMI, age menopause, HRT	Borderline ovarian tumors versus disease free controls	1
Royar, 2001[141]	Cases: 282 Controls: 533	1 to 2 yr 3 to 5 yr 6 to 10 yr 11 to 15 yr 16 to 20 yr 21+ yr	0.89 0.45 0.37 0.42 0.32 0.12	0.47 to 1.67 0.22 to 0.92 0.22 to 0.79 0.22 to 0.79 0.14 to 0.73 0.03 to 0.53	Parity, family history, breastfeeding , tubal ligation, hysterectomy		1
Riman, 2002[134]	Cases: 655 Controls: 3899	<2y 2 to 4 y 5 to 9 y ≥10 y	0.95 0.88 0.5 0.36	0.71 to 1.26 0.61 to 1.25 0.32 to 0.80 0.22 to 0.59	Age, parity, BMI, age menopause, HRT		1

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Schildkraut, 2002[29]	Cases: 22 Controls: 351	3 to 18 mo 19 to 59 mo >60 mo	0.4 0.3 0.2	0.2 to 0.8 0.2 to 0.7 0.1 to 0.5	Age	High progestin	4
	Cases: 71 Controls: 831	3 to 18 mo 19 to 59 mo >60 mo	0.6 0.5 0.4	0.4 to 0.9 0.3 to 0.7 0.2 to 0.6	Age	High potency estrogen	4
	Cases: 82 Controls: 803	3 to 18 mo 19 to 59 mo >60 mo	0.7 0.7 0.4	0.4 to 1.0 0.4 to 1.0 0.2 to 0.6	Age	Low potency progestins	4
	Cases: 33 Controls: 323	3 to 18 mo 19 to 59 mo >60 mo	0.5 0.8 0.3	0.3 to 1.0 0.5 to 1.5 0.1 to 0.6	Age	Low potency estrogen	4
Walker, 2002[158]	Cases: 692 Controls: 1279	≤48 mo 49+ mo Never OC use	0.72 0.51 1	0.59 to 0.88 0.40 to 0.65	Age, race, parity, BTL	No family history of ovarian cancer	2
	Cases: 33 Controls: 24	≤48 mo use 49+ mo use Never use	0.34 0.07 1	0.08 to 1.55 0.01 to 0.44	Age, race, parity, BTL	Positive family history of ovarian cancer	2
Tung, 2003[152]	Cases: 603 Controls: 607	<1.5 yr 1.6 to 5 yr >5 yr	0.8 0.6 0.4	0.5 to 1.1 0.4 to 0.8 0.3 to 0.6	Age, race, parity, study site, education, tubal ligation		1
McGuire, 2004[115]	Cases: 36 Controls: 568	<1 year 1 to 2 yr 3 to 6 yr ≥ yr	1.00 1.18 0.46 0.22	Reference 0.50 to 2.75 0.16 to 1.28 0.07 to 0.71	Age, race, parity	Cases with BRCA1 mutations (N=36)	4
	Cases: 381 Controls: 568	<1 year 1 to 2 yr 3 to 6 yr ≥7 yr	1.00 0.81 0.48 0.43	Reference 0.55 to 1.19 0.32 to 0.72 0.30 to 0.63	Age, race, parity	Cases without BRCA1 mutations (N=381)	4

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Mills, 2004[117]	Cases: 256 Controls: 1122	≤1 year 2 to 5 yr 6 to 10 yr >10 yr	0.89 0.82 0.62 0.37	0.59 to 1.36 0.55 to 1.21 0.38 to 1.00 0.20 to 0.68	Age, race, breastfeeding		1
	Cases: 182 Controls: 1122	≤1 year 2 to 5 yr 6 to 10 yr >10 yr	0.90 0.74 0.67 0.26	0.56 to 1.46 0.46 to 1.18 0.39 to 1.15 0.12 to 0.60	Age, race, breastfeeding	Invasive ovarian cancer (N=182)	1
	Cases: 74 Controls: 1122	≤1 year 2 to 5 yr 6 to 10 yr >10 yr	0.93 1.00 0.57 0.67	0.45 to 1.93 0.57 to 2.07 0.23 to 1.42 0.27 to 1.68	Age, race, breastfeeding	Borderline ovarian cancer (N=74)	1
Pike, 2004[130]	Cases: 477 Controls: 660	<5 yr 5 to 9 yr 10+ yr	1.0 0.72 0.48	0.72 to 1.39 0.46 to 1.13 0.29 to 0.78	Age, race, parity, menopausal status, BMI, family history, SES, education, age at last birth, gravidity, OC use		2
Quirk, 2004[132]	Cases: 418 Controls: 836	≤5 yr >5 yr	1.22 1.18	0.84 to 1.79 0.78 to 1.79	Age, parity, family history, history of tubal ligation, noncontraceptive estrogen use		2
Tavani, 2004[147]	Cases: 1031 Controls: 2411	60+ mo <60 mo or never	1 2.01	Reference 1.11 to 3.66	Age, center, year at interview, education		2
Whittemore, 2004[159]	Cases: 147 Controls: 304	<1 year 1 to 2 yr 3 to 5 yr 6+ yr	1.0 1.5 0.69 0.62	Reference 0.82 to 2.9 0.33 to 1.4 0.35 to 1.1	Age, parity, study center	BRCA1 and BRCA2 carriers	4

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Greer, 2005[91]	Cases: 364 Controls: 529	< 5 yr 5+ yr	0.39 0.22	0.18 to 0.85 0.12 to 0.43	Age, parity, family history, tubal ligation	Compared never users to both androgenic and nonandrogenic OC users	2
	Cases: 405 Controls: 592	< 5 yr 5+ yr	0.58 0.35	0.37 to 0.93 0.2 to 0.61	Age, parity, family history, tubal ligation	Compared never users to androgenic only OC users	2
	Cases: 381 Controls: 761	< 5 yr 5+ yr	0.56 0.73	0.41 to 0.76 0.5 to 1.07	Age, parity, family history, BTL	Compared never users to nonandrogenic only OC users	2
Greer, 2005[92]	Cases: 715 Controls: 1631	Single episode; 1 to 6 mo Single episode; 7 to 12 mo Single episode; ≥13 mo ≥1 episode; 1 to 6 mo ≥1 episode; 7 to 12 mo ≥1 episode; ≥13 mo	0.71 1.04 0.66 0.71 0.97 0.62	0.50 to 0.99 0.66 to 1.63 0.48 to 0.90 0.51 to 0.99 0.64 to 1.47 0.48 to 0.81	Age	Parous women	4
	Cases: 608 Controls: 926	Single episode use: 1 to 6 mo Single episode use: 7 to 12 mo Single episode use: ≥13 mo >1 episode of use: 1 to 6 mo >1 episode of use: 7 to 12 mo >1 episode of use: ≥13 mo	.73 1.0 .63 .75 .96 .56	.54 to .99 .67 to 1.50 .48 to 82 .56 to 1.0 .66 to 1.38 .45 to .71	Age, parity		4
	Cases: 216 Controls: 168	Single episode; 1 to 6 mo Single episode; 7 to 12 mo Single episode; ≥13 mo ≥1 episode; 1 to 6 mo ≥1 episode; 7 to 12 mo ≥1 episode; ≥13 mo	1.04 1.08 0.84 1.05 1.08 0.68	0.52 to 2.08 0.42 to 2.78 0.46 to 1.56 0.55 to 2.01 0.49 to 2.34 0.42 to 1.11	Age	Nulliparous women	4

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Tung, 2005[153]	Cases: 558 Controls: 607	0.1 to 1.8 yr (all women) 1.9 to 5.3 yr (all women) 5.4+ yr (all women) 0.1 to 1.8 yr (premenopausal women) 1.9 to 5.3 yr (premenopausal women) 5.4+ yr (premenopausal women) 0.1 to 1.8 yr (postmenopausal women) 1.9 to 5.3 yr (postmenopausal women) 1.9 to 5.3 yr (postmenopausal women)	0.74 0.60 0.45 0.52 0.34 0.28 0.75 0.86 0.58	0.50 to 1.07 0.41 to 0.88 0.30 to 0.69 0.30 to 0.90 0.19 to 0.61 0.15 to 0.52 0.43 to 1.29 0.51 to 1.45 0.31 to 1.08	Age, race, parity, study center, education, BTL, HRT, ovulation variables	Data presented as whole sample and subgrouped by menopausal status (pre/post)	6[152]
Gronwald, 2006[94]	Cases: 150 Controls: 150	≤2 yr >2 yr	0.8 0.2	0.2 to 2.5 0.1 to 0.7	NR	BRCA1 carriers	2
Huusom, 2006[107]	Cases: 202 Controls: 1564	<1 year 1 to 4 yr 5 to 9 yr 10+ yr	1.39 1.00 1.23 0.77	0.77 to 2.54 Reference 0.70 to 2.16 0.45 to 1.34	Age, parity, smoking, breastfeeding , age at first birth, duration of contraception use, intake of milk		2
McLaughlin, 2007[118]	Cases: 128 Controls: 380	0 to 1.0 yr 1.1 to 3.0 yr 3.1 to 5.0 yr >5.0 yr	0.56 0.42 0.14 0.37	0.28 to 1.10 0.20 to 0.88 0.05 to 0.46 0.19 to 0.72	Parity, breastfeeding , tubal ligation, ethnicity	BRCA2 carriers only	4
	Cases: 799 Controls: 2424	0 to 1.0 yr 1.1 to 3.0 yr 3.1 to 5.0 yr >5.0 yr	0.67 0.63 0.36 0.47	0.50 to 0.89 0.46 to 0.86 0.25 to 0.53 0.35 to 0.62	Parity, breastfeeding , tubal ligation, ethnicity	All cases and controls have BRCA1 and/or BRCA2 mutations	4
	Cases: 670 Controls: 2043	0 to 1.0 yr 1.1 to 3.0 yr 3.1 to 5.0 yr >5.0 yr	0.69 0.67 0.41 0.48	0.50 to 0.95 0.47 to 0.96 0.27 to 0.63 0.35 to 0.66	Parity, breastfeeding , tubal ligation, ethnicity	BRCA1 carriers only	4

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Soegaard, 2007[146]	Cases: 50 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 1.60 0.95 1.32	Reference 0.45 to 5.65 0.20 to 4.49 0.38 to 4.64	Age, parity	Mucinous tumors	3
	Cases: 86 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 0.88 0.36 0.37	Reference 0.38 to 2.03 0.10 to 1.29 0.14 to 0.99	Age, parity	"Other" tumors	3
	Cases: 554 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 0.90 0.40 0.40	Reference 0.63 to 1.30 0.24 to 0.66 0.26 to 0.60	Age, parity		3
	Cases: 343 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 0.80 0.42 0.31	Reference 0.52 to 1.23 0.23 to 0.74 0.18 to 0.51	Age, parity	Serous tumors	3
	Cases: 75 Controls: 1564	<2 yr 2 to 5 yr 6 to 9 yr 10+ yr	1.0 1.27 0.15 0.62	Reference 0.53 to 3.05 0.02 to 1.18 0.24 to 1.62	Age, parity	Endometrioid tumors	3
Jordan, 2008[109]	Cases: 627 Controls: 1508	1 to 12 mo 13 to 60 mo 61 to 120 mo 212 to 180 mo 181 to 240 mo >240 mo per year	1.02 0.71 0.52 0.51 0.36 0.22 0.95	0.72 to 1.44 0.53 to 0.95 0.38 to 0.70 0.36 to 0.73 0.23 to 0.58 0.12 to 0.42	Parity, family history, BTL, OC use, hysterectomy, education		1
Lurie, 2008[114]	Cases: 813 Controls: 993	<1 year 1 to 2 yr 3 to 6 yr 7 to 9 yr ≥10 yr	0.74 0.47 0.59 0.49 0.30	0.53 to 1.01 0.33 to 0.67 0.42 to 0.81 0.31 to 0.78 0.19 to 0.47	Age, race, menopausal status, family history, education, tubal ligation, gravidity, age at last pregnancy, type of menopause, age at menopause, use of menopausal hormones		1

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Moorman, 2008[121]	Cases: 314 Controls: 360	<1 year 1 to <5 yr 5 to 10 yr >10 yr	0.8 0.6 0.5 0.3	0.4 to 1.7 0.4 to 1.0 0.3 to 0.9 0.2 to 0.6	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Premenopausal women	4
	Cases: 582 Controls: 607	<1 year 1 to <5 yr 5 to 10 yr >10 yr	1.1 0.7 0.8 0.9	0.7 to 1.6 0.5 to 1.0 0.6 to 1.2 0.6 to 1.5	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Postmenopausal women	4
Grant, 2010[90]	Cases: 62 Controls: 1086	0 to <1 yr 1 to <5 yr 5+ yr	0.63 0.80 1.13	0.24 to 1.71 0.38 to 1.70 0.56 to 2.26	Age	Serous primary peritoneal cancer	4
	Cases: 495 Controls: 1086	0 to <1 yr 1 to <5 yr 5+ yr	1.14 0.82 0.74	0.79 to 1.65 0.61 to 1.11 0.55 to 1.00	Age	Serous ovarian cancer	4
Ness, 2011[123]	Cases: 869 Controls: 1779	OCs for contraception ≤4 yr OCs for contraception 5 to 9 yr OCs for contraception ≥10 yr OCs for noncontraception ≤4 yr OCs for noncontraception 5 to 9 yr OCs for noncontraception ≥10 yr OCs for both ≤4 yr OCs for both 5 to 9 yr OCs for both ≥10 yr	0.91 0.78 0.52 0.93 1.60 0.53 1.22 0.72 0.40	0.75 to 1.10 0.59 to 1.05 0.35 to 0.76 0.64 to 1.36 0.58 to 4.47 0.11 to 2.62 0.87 to 1.73 0.46 to 1.12 0.25 to 0.67	Age, race, family history, number of pregnancies, infertility		4
Wilailak, 2012[160]	Cases: 330 Controls: 982	1 to 12 months 13 to 24 months 25 to 26 months >36 months	0.86 0.84 0.56 0.43	0.61 to 1.20 0.47 to 1.51 0.28 to 1.14 0.29 to 0.64			1
Cohort							
Hankinson, 1995[98]	Exposed: 592,056 person-yr Unexposed: 599,301 person-yr	Past <1 yr Past 1 to <3 yr Past 3 to <5 yr Past ≥5 yr Current	1.21 1.09 0.8 0.65 1.92	0.8 to 1.86 0.69 to 1.71 0.42 to 1.52 0.4 to 1.05 0.69 to 5.33	Age, parity, smoking, BTL, age at menopause, Quetelet's Index		7
Vessey, 1995[157]	Exposed: 3520 Unexposed: 5881	Up to 48 total mo of use 49 to 96 total mo of use 97+ mo of use	1.0 0.3 0.3	0.4 to 2.5 0.0 to 1.1 0.1 to 0.7	Age, parity		7

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Kumle, 2004[110]	Exposed: 75,533 Unexposed: 28,019	<1 yr 1 to 4 yr 5 to 9 yr 10 to 14 yr 15+ yr Current Former	0.9 0.5 0.6 0.5 0.1 0.5 0.6	0.5 to 1.4 0.4 to 0.8 0.4 to 0.9 0.3 to 1.0 0.01 to 0.6 0.2 to 0.9 0.5 to 0.8	Age, parity, menopausal status, HRT, country		1
		Current Former <1 year 1 to 4 yr 5 to 9 yr 10 to 14 yr 15+ yr per year	0.5 0.7 0.2 0.6 0.7 0.9 NR 0.96	0.2 to 1.6 0.5 to 1.2 0.1 to 1.0 0.3 to 1.2 0.4 to 1.4 0.4 to 2.0 NR 0.91 to 1.0	Age, parity, menopausal status, HRT, country	Borderline ovarian cancer only	1
		<1 yr 1 to 4 yr 5 to 9 yr 10 to 14 yr 15+ yr Current Former	1.2 0.5 0.6 0.3 0.1 0.4 0.6	0.7 to 2.0 0.3 to 0.8 0.3 to 0.9 0.1 to 0.8 0.02 to 0.8 0.2 to 1.0 0.4 to 0.8	Age, parity, menopausal status, HRT, country	Invasive ovarian cancer only	1
Vessey, 2006[156]	Exposed: 301,000 person-years Unexposed: 187,000 person-years	up to 48 mo 48 to 96 mo 97+ mo	1.0 0.3 0.3	0.6 to 1.7 0.1 to 0.6 0.1 to 0.5	Age, parity, BMI, smoking, social class, height, age at first term pregnancy, age at first marriage	Ovarian cancer	2
Hannaford, 2007[37]	Exposed: 744,000 person-years of observation Unexposed: 339,000 person-years of observation	<48 mo 49 to 96 mo >96 mo	0.58 0.57 0.38	0.33 to 1.04 0.30 to 1.07 0.16 to 0.88	Age, parity, smoking, social status, ever use of HRT	General practitioner dataset	1

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Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Tworoger, 2007[154]	Exposed: 41,125 Unexposed: 54,027	≤3 yr >3 to 5 yr >5 to 10 yr >10 yr	1.12 0.97 0.75 0.62	0.90 to 1.38 0.66 to 1.41 0.54 to 1.05 0.37 to 1.04	Age, parity, menopausal status, BMI, age at menarche, smoking, BTL and HRT use		1
Antoniou, 2009[81]	Exposed: 2415 Unexposed: 766	>0 to 1 yr >1 to 3 yr >3 to 5 yr >5 yr	1.04 0.60 0.41 0.35	0.66 to 1.62 0.35 to 1.03 0.19 to 0.87 0.22 to 0.55	Parity	BRCA1 and BRCA2 mutation carriers	4
	Exposed: 1655 Unexposed: 512	>0 to 1 year >1 to 3 yr >3 to 5 yr >5 yr	1.03 0.51 0.40 0.34	0.64 to 1.65 0.28 to 0.93 0.17 to 0.91 0.21 to 0.54	Parity	BRCA1 mutation carriers	4
	Exposed: 760 Unexposed: 245	>0 to 5 yr >5 yr	1.33 0.59	0.52 to 3.39 0.16 to 2.24	Parity	BRCA2 mutation carriers	4
Dorjgochoo, 2009[88]	Exposed: 12,957 Unexposed: 15,557	<2 yr ≥2 yr	1.58 0.65	0.89 to 2.83 0.29 to 1.44	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods	Only reporting for women using OC as others in the cohort used other forms of contraception.	2
Rosenblatt, 2009[138]	Exposed: 352,695 person-years Unexposed: 2,057,377 person-years	1 to 11 mo 12 to 59 mo 60+ mo	1.36 0.82 1.44	0.87 to 2.13 0.47 to 1.41 0.87 to 2.39	Age, parity, use of injectable contraceptives		1
Braem, 2010[85]	Exposed: 8,668 person-years Unexposed: 25,916 person-years	≤5 yr >5 yr per year	0.92 0.47 0.95	0.61 to 1.38 0.30 to 0.76 0.91 to 0.99	Age, parity		2

00803320

Table 6. Data for outcomes on duration of OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Tsilidis, 2011[151]	Exposed: 67,870 women OC exposed Unexposed: 100,304 women OC unexposed	≤1 yr 2 to 4 yr 5 to 9 yr ≥10 yr	1.00 1.05 0.80 0.55	Reference 0.79 to 1.38 0.59 to 108 0.41 to 0.75	Age, parity, menopausal status, BMI, smoking, center, unilateral oophorectomy, hysterectomy, menopausal hormones, age at menarche		3
Yang, 2012[162]	Exposed: 192,836 women OC exposed Unexposed: 132,923 women OC unexposed	1 to 4 yr 5 to 9 yr ≥10 yr	0.82 0.78 0.56	0.67 to 1.00 0.62 to 0.98 0.42 to 0.75	Age, parity, menopausal hormone therapy		1

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; GCT = granulosa cell tumor; HRT = hormone replacement therapy; IUD = intrauterine device; mo = month/months; OC = oral contraceptive; OR = odds ratio; NR = not reported; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR=1.0.

[c]Meta-analysis code:1=Included in this meta-analysis; 2=Excluded due to less than three duration categories; 3=Excluded due to never use is not the reference group; 4=Excluded due to odds ratios only provided for subpopulations; 5=Excluded due to odds ratios only provided per year of OC use; 6=Excluded due to study is grouped with another included article also reporting duration data; 7=Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

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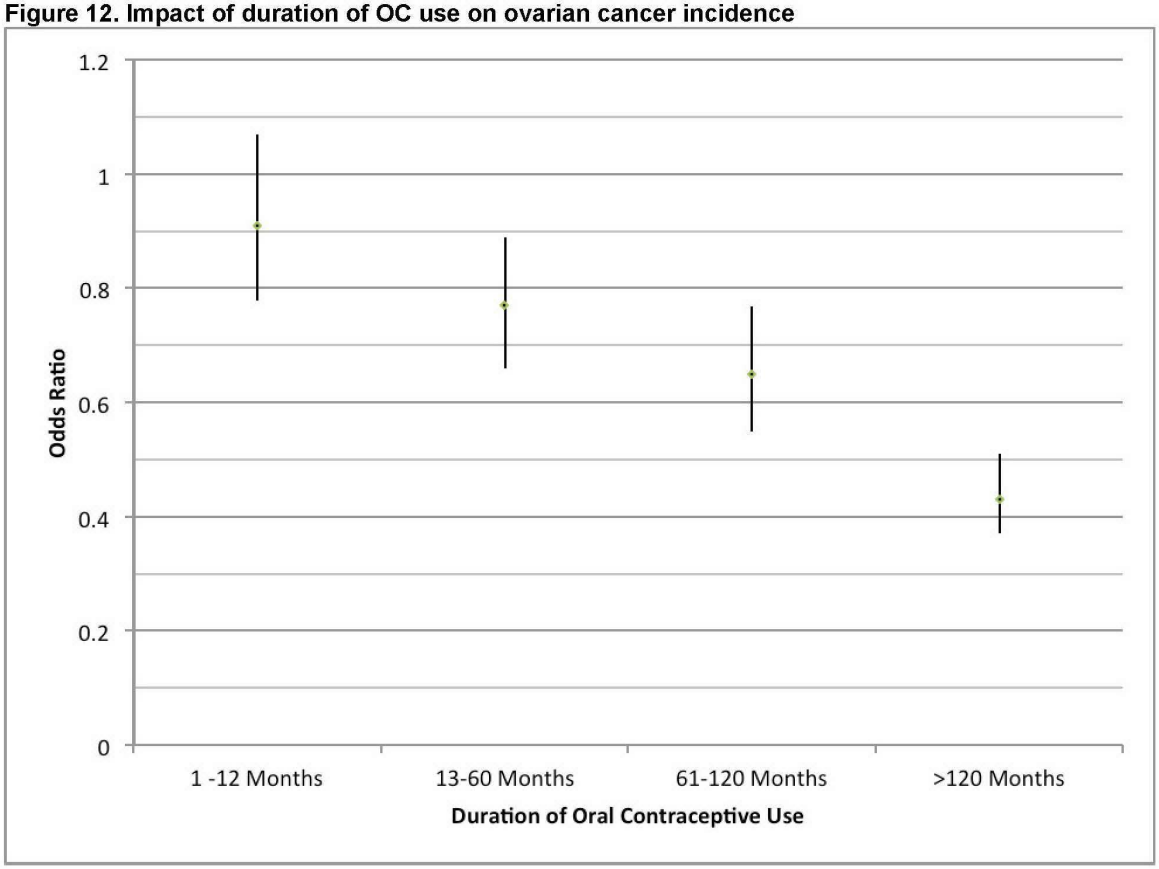
Table 7 and Figure 12 show the odds ratios for the meta-analysis of duration of OC use. These findings indicate a significant duration-response relationship between OC use and ovarian cancer incidence, with higher levels of protection afforded to women who use OCs for longer duration. Women using oral contraceptives for 10 or more years show a reduction in ovarian cancer incidence of more than 50 percent. There is no evidence of heterogeneity. The estimated value of σ is 0.15.

Table 7. Estimated odds ratios by duration of OC use (ovarian cancer incidence)

Duration Interval	Odds Ratio (95% Confidence Interval)	P-Value
1–12 months	0.91 (0.78 to 1.07)	0.2504
13–60 months	0.77 (0.66 to 0.89)	0.0014
61–120 months	0.65 (0.55 to 0.77)	<0.0001
>120 months	0.43 (0.37 to 0.51)	<0.0001

Figure 12. Impact of duration of OC use on ovarian cancer incidence



Pooled Analyses

Four pooled analyses[21,23,105,120] reported on duration of OC use but did not meet criteria for inclusion in the meta-analysis. The three largest of these studies reported a significantly lower incidence of ovarian cancer following longer duration of OC use.[21,23,120] The one remaining study[105] examined only OC use of less than or greater than 1 year and did not identify a clear trend.

Sensitivity Analyses

We repeated our analyses excluding the 10 studies not conducted within the United States. The estimates for the remaining 5 studies (3 case-control and 2 cohort) were 0.84 (95% CI, 0.67 to 1.05) for <1 year duration, 0.72 (CI, 0.59 to 0.89) for 1 to 5 years' duration, 0.64 (CI, 0.51 to 0.81) for >5 to 10 years' duration, and 0.42 (CI, 0.32 to 0.56) for >10 years' duration.

We also performed analyses for studies published from 1990 forward (18 studies, 13 case-control and 5 cohort). The estimates were 0.93 (95% CI, 0.81 to 1.06) for <1 year duration, 0.81 (CI, 0.72 to 0.91) for 1 to 5 years' duration, 0.65 (CI, 0.56 to 0.75) for >5 to 10 years' duration, and 0.44 (CI, 0.39 to 0.51) for >10 years' duration.

We also conducted a sensitivity analysis in which we included the large pooled analysis by Beral et al.[21] but excluded the individual studies from our meta-analysis that had been included in their pooled analysis.[87,110,118,125,133,141] The estimates were 0.91 (95% CI, 0.75 to 1.09) for <1 year duration, 0.75 (CI, 0.63 to 0.91) for 1 to 5 years' duration, 0.57 (CI, 0.47 to 0.69) for >5 to 10 years' duration, and 0.43 (CI, 0.35 to 0.51) for >10 years' duration, similar to the estimates from the main meta-analysis.

Age at First OC Use

Six studies[110,114,121,125,141,144,145] were included in the primary meta-analysis examining the effect of age at first OC use on ovarian cancer incidence. Of these, 5 were case-control studies representing 3,552 cases and 4,713 controls, and 1 was a cohort study representing 103,552 participants. Four studies were rated good quality and 2 fair quality. Abstracted data not included in this analysis are specified (with rationale) in Table 8. Reasons for exclusion from this analysis included the following: reporting data for fewer than three age categories; providing odds ratios for subpopulations only; or in one instance,[100] not meeting publication date criteria to include in the primary meta-analysis.

Table 8. Data for outcomes on age at first OC use (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons (Age in Years)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control							
Harlow, 1991[100]	Cases: 194 Controls: 193	<21 22 to 26 >26	0.8 0.7 0.8	0.4 to 1.8 0.3 to 1.4 0.4 to 1.4	Age, parity, religion		4
Ness, 2000[125]	Cases: 767 Controls: 1367	<20 20 to 24 25 to 29 30 to 34 ≥35	0.6 0.6 0.5 0.8 0.8	0.4 to 0.8 0.5 to 0.8 0.4 to 0.8 0.5 to 1.2 0.4 to 1.3	Age, race, family history, number of pregnancies		1
	Cases: 616 Controls: 1367	<20 20 to 24 25 to 29 30 to 34 ≥35	1.0 1.0 0.8 0.9 0.8	Reference 0.7 to 1.4 0.5 to 1.2 0.5 to 1.7 0.4 to 1.7	Age, race, family history, number of pregnancies	Invasive ovarian cancer (N=616)	1
	Cases: 151 Controls: 1367	<20 20 to 24 25 to 29 30 to 34 ≥35	1.0 1.0 0.5 0.8 0.7	Reference 0.6 to 1.6 0.2 to 1.2 0.3 to 2.5 0.2 to 2.7	Age, race, family history, number of pregnancies	Borderline ovarian cancer (N=151)	1
Siskind, 2000[145]	Cases: 794 Controls: 853	<20 20 to 24 25 to 29 30 to 34 >35	1.0 1.34 1.82 2.1 1.66	Reference 0.82 to 2.2 0.96 to 3.4 0.98 to 4.6 0.68 to 4.0	Duration of use, overall and before 1st pregnancy, age at first use, time since last use		1
Royar, 2001[141]	Cases: 282 Controls: 533	14 to 16 17 to 19 20 to 24 25 to 29 30+	0.31 0.18 0.20 0.40 0.69	0.12 to 0.80 0.08 to 0.40 0.10 to 0.45 0.21 to 0.76 0.42 to 1.11	Parity, family history, breastfeeding, tubal ligation, hysterectomy		1

Table 8. Data for outcomes on age at first OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Age in Years)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Greer, 2005[91]	Cases: 405 Controls: 592	<20 >20	0.42 0.51	0.23 to 0.75 0.32 to 0.79	age, parity, family history, tubal ligation	Compared never users to androgenic only OC users	2, 3
	Cases: 381 Controls: 761	<20 ≥20	0.54 0.63	0.34 to 0.85 0.47 to 0.85	Age, parity, family history, BTL	Compared never users to nonandrogenic only OC users	2, 3
	Cases: 364 Controls: 529	<20 20+	0.26 0.28	0.13 to 0.52 0.13 to 0.58	Age, parity, family history, tubal ligation	Compared never users to both androgenic and nonandrogenic OC users	2, 3
Lurie, 2008[114]	Cases: 813 Controls: 993	<20 20 to 24 25 to 29 ≥30	0.39 0.59 0.54 0.58	0.27 to 0.56 0.44 to 0.79 0.37 to 0.79 0.39 to 0.86	Age, race, menopausal status, family history, education, tubal ligation, gravidity, age at last pregnancy, type of menopause, age at menopause, use of menopausal hormones		1
Moorman, 2008[121]	Cases: 314 Controls: 360	<20 20 to 24 25 to 29 >29	0.5 0.5 0.4 1.2	0.3 to 0.8 0.3 to 0.9 0.2 to 1.0 0.3 to 4.4	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Premenopausal women	1
	Cases: 582 Controls: 607	<20 20 to 24 25 to 29 >29	0.9 0.8 0.8 0.9	0.5 to 1.3 0.6 to 1.1 0.5 to 1.2 0.6 to 1.4	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Postmenopausal women	1

Table 8. Data for outcomes on age at first OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Age in Years)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort							
Kumle, 2004[110]	Exposed: 75,533 Unexposed: 28,019	<20 20 to 24 25+	0.5 0.4 0.7	0.3 to 1.0 0.3 to 0.7 0.5 to 1.1	Age, parity, menopausal status, HRT, country	Invasive ovarian Cancer only	1
	Exposed: 75,533 Unexposed: 28,019	<20 20 to 24 25+	0.4 0.8 0.8	0.2 to 0.9 0.5 to 1.4 0.4 to 1.4	Age, parity, menopausal status, HRT, country	Borderline ovarian cancer only	1
	Exposed: 75,533 women exposed Unexposed: 28,019 women unexposed	<20 yr 20 to 24 25+	0.6 0.7 1.0	0.3 to 1.0 0.5 to 1.1 0.6 to 1.5	Age, parity, menopausal status, HRT, country, duration of use		1
Antoniou, 2009[81]	Exposed: 2415 Unexposed: 766	Never <20 20 to 24 ≥25	1.72 1.00 0.88 0.96	1.05 to 2.82 Reference 0.51 to 1.50 0.53 to 1.73	Parity	BRCA1 and BRCA2 mutation carriers	2
	Exposed: 1655 Unexposed: 512	Never <20 20 to 24 ≥25	1.75 1.00 0.86 0.87	1.05 to 2.90 Reference 0.49 to 1.50 0.46 to 1.65	Parity	BRCA1 mutation carriers	2
	Exposed: 760 Unexposed: 245	Never <20 >20	1.25 1.00 1.46	0.31 to 5.08 Reference 0.35 to 6.01	Parity	BRCA2 mutation carriers	2

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Table 8. Data for outcomes on age at first OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Age in Years)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Dorjgochoo, 2009[88]	Exposed: 12,957 Unexposed: 15,557	<29 ≥29	1.26 0.99	0.64 to 2.46 0.51 to 1.92	Parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods		3
Braem, 2010[85]	Exposed: 8,668 person-years Unexposed: 25,916 person-years	≤40 >40	1.0 1.28	Reference 0.68 to 2.43	Age, parity, duration of OC use		3

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; GCT = granulosa cell tumor; HRT = hormone replacement therapy; IUD = intrauterine device; NR=not reported; OC = oral contraceptive; OR = odds ratio

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR=1.0.

[c]Meta-analysis code: 1=Included in this meta-analysis; 2=Excluded due to odds ratios provided for subpopulations only; 3=Excluded due to less than three age-at-first-use categories provided; 4=Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

00803327

Table 9 lists the odds ratios for the meta-analysis of age at first OC use. The results show a relatively strong relationship between age at first use and ovarian cancer incidence, although confidence intervals overlap. If there is an effect of earlier age, it is unclear whether the relation is linear or whether there is a threshold effect (i.e., less protection in women who start OCs after age 30). Unfortunately, most studies did not control for duration of use. This potential confounder lessens the strength of this finding.

Table 9. Estimated odds ratios by age at first OC use (ovarian cancer incidence)

Age Interval	Odds Ratio (95% Confidence Interval)	P-Value
< 20 years	0.63 (0.45 to 0.89)	0.018
20–24 years	0.71 (0.51 to 0.99)	0.044
25–30 years	0.67 (0.46 to 0.99)	0.045
> 30 years	0.89 (0.60 to 1.32)	0.489

Pooled Analyses

Two pooled analyses[21,23] reported on age at first use, with none reporting significant trends. One study[21] reported that there was no heterogeneity in the decline in relative risk of ovarian cancer with increasing duration of use across women who started OCs at different ages.

Sensitivity Analyses

We repeated our analyses excluding the three studies not conducted within the United States. The estimates for the remaining three studies, all case-control, were 0.70 (95% CI, 0.27 to 1.75) for age <20 years, 0.86 (CI, 0.34 to 2.20) for age 20 to <24 years, 0.83 (CI, 0.30 to 2.27) for age 24 to <30 years, and 0.93 (CI, 0.33 to 1.67) for age ≥30 years.

We also performed analyses for studies published from 1990 forward (7 studies, 6 case-control and 1 cohort). The estimates were 0.64 (95% CI, 0.47 to 0.87) for age <20 years, 0.71 (CI, 0.53 to 0.96) for age 20 to <24 years, 0.67 (CI, 0.48 to 0.95) for age 24 to <30 years, and 0.89 (CI, 0.63 to 1.28) for age ≥30 years.

Time Since Last OC Use

Eight studies[37,110,114,121,125,133,134,141,154] were included in this meta-analysis examining the effect of time since last OC use on ovarian cancer incidence. Of these, 5 were case-control studies representing 3606 cases and 7759 controls, and 3 were cohort studies representing 198,704 participants and 1,083,000 person years. Four studies were rated good quality and 4 fair quality. Abstracted data not included in this analysis are specified (with rationale) in Table 10. Reasons for exclusion from this analysis included the following: using fewer than three comparisons; presenting categories that were not amenable to a combined analysis; and reporting time since last use data from the same study as another article already included in the analysis (Table 10). None of the three pooled analyses reporting on time since last use met inclusion criteria for meta-analysis.

Table 10. Data for outcomes on time since last OC use (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons (Time Since Last Use)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control							
Rosenblatt, 1992[140]	Cases: 393 Controls: 2561	1 to 24 mo 25 to 84 mo 85 to 132 mo 133+ mo	0.69 0.76 0.88 0.44	0.26 to 1.82 0.35 to 1.68 0.38 to 2.05 0.22 to 0.99	Age, center, years of disease, live births	High dose	4
		1 to 24 mo 25 to 84 mo 85 to 132 mo 133+ mo	1.45 0.70 0.77 0.48	0.74 to 2.85 0.28 to 1.75 0.27 to 2.21 0.16 to 1.39	Age, center, years of disease, live births	Low dose	4
Rosenberg, 1994[137]	Cases: 441 Controls: 2065	<15 yr 15 to 19 yr 20+	0.4 0.5 0.8	0.2 to 0.8 0.3 to 1.0 0.4 to 1.5	Parity, hysterectomy, BTL, removal of one ovary, race, family history, age, geographic area		4
Wittenberg, 1999[161]	Cases: 322 Controls: 426	≤5 yr 6 to 15 yr 15+ yr	0.6 0.6 1.2	0.2 to 2.2 0.2 to 1.7 0.5 to 2.9	Age, parity, duration of use	Mucinous ovarian cases	4
	Cases: 322 Controls: 426	≤5 yr 6 to 15 yr 15+ yr	0.6 0.6 1.1	0.3 to 1.3 0.3 to 1.0 0.7 to 1.7	Age, parity, duration of use	Nonmucinous cases	4
Huusom, 2000[107]	Cases: 202 Controls: 1564	0 to 10 yr 11 to 20 yr 21+ yr	1 1.59 1.63	Reference 0.80 to 3.16 0.72 to 3.70	Age, childbirth, additional births, first birth, breastfeeding, duration of use, smoking, intake of milk	Borderline ovarian cancer	2
Ness, 2000[125]	Cases: 767 Controls: 1367	<10 yr 10 to 19 yr 20 to 29 yr ≥30 yr	0.4 0.6 0.6 1.0	0.3 to 0.6 0.4 to 0.8 0.5 to 0.8 0.6 to 1.4	Age, number of pregnancies, family history of ovarian cancer, race		1
Sanderson, 2000[143]	Cases: 276 Controls: 388	Never or < 3 mo <10 yr 10+ yr	1 0.7 0.8	Reference 0.4 to 1.3 0.5 to 1.2	Age, parity		2
Siskind, 2000[145]	Cases: 794 Controls: 853	<1 yr 1 to <5 yr 5 to <10 yr 10 to <20 yr 20+ yr	0.78 1.46 1.02 1.4 1	0.30 to 2.0 0.58 to 3.6 0.48 to 2.2 0.91 to 2.1 Reference			3

Table 10. Data for outcomes on time since last OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Time Since Last Use)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Chiaffarino, 2001[87]	Cases: 1031 Controls: 2411	<10 yr ≥10 yr	0.5 0.5	0.2 to 1.1 0.2 to 1.2	Age, parity, family history, center, education		2
Royar, 2001[141]	Cases: 282 Controls: 533	0 yr 1 to 5 yr 6 to 10 yr 11 to 20 yr 21+ yr	0.17 0.34 0.49 0.45 0.52	0.07 to 0.43 0.16 to 0.73 0.23 to 1.03 0.28 to 0.73 0.28 to 0.96	Parity, breastfeeding, family history, BTL, hysterectomy		1
Riman, 2002[134]	Cases: 655 Controls: 3899	<15 yr 15 to 19 yr 20 to 24 yr 25+ yr	0.45 0.66 0.71 0.9	0.27 to 0.73 0.43 to 0.99 0.51 to 0.99 0.27 to 1.22	Age, parity, BMI, age of menopause		1
Riman, 2001[133]	Cases: 193 Controls: 3899	<15 yr 15 to 19 yr 20 to 24 yr 25+ yr	1.16 1.67 0.92 1.14	0.45 to 3.02 0.74 to 3.80 0.43 to 1.94 0.62 to 2.10	Age, parity, BMI, age of menopause, ever use of unopposed estrogen, estrogens with cyclic progestins, estrogens with continuous progestins	Borderline ovarian cancer	1
Lurie, 2008[114]	Cases: 813 Controls: 993	≤5 yr 6 to 9 yr 10 to 19 yr 20 to 29 yr 30+yr	0.19 0.33 0.47 0.64 0.72	0.12 to 0.30 0.16 to 0.67 0.33 to 0.68 0.48 to 0.86 0.49 to 1.06	Formulation potency and duration of use, age, race, menopausal status, family history, education, tubal ligation, gravidity, age at last pregnancy, type of menopause, age at menopause, use of menopausal hormones		1
Moorman, 2008[121]	Cases: 314 Controls: 360	<5 yr 5+ to <10 yr 10 to 20 yr >20 yr	0.3 0.4 0.6 0.8	0.2 to 0.6 0.2 to 0.9 0.3 to 1.0 0.5 to 1.4	Age, race, parity, BMI, family history, tubal ligation, infertility, age at last pregnancy	Premenopausal women only	1

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Table 10. Data for outcomes on time since last OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Time Since Last Use)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort							
Hankinson, 1995[98]	Exposed: 592,056 person-years Unexposed: 599,301 person-years	Current <5 yr 5 to <10 yr 10 to <15 yr 15+ yr	1.86 0.86 0.77 1.01 1.11	0.67 to 5.19 0.48 to 1.56 0.48 to 1.26 0.66 to 1.54 0.68 to 1.81	Age, parity, BTL, age at menarche, age at menopause, smoking, Quetelet's index		5
Vessey, 1995[157]	Exposed: 3520 Unexposed: 5881	≤48 mo 49 to 96 mo 97+ mo	0.1 0.3 0.8	0 to 0.5 0 to 1.1 0.4 to 1.7	Age, parity		4
Kumle, 2004[110]	Exposed: 75,533 Unexposed: 28,019	0 to 9 yr 10 to 14 yr 15 to 19 yr 20+	0.5 0.5 0.6 0.6	0.3 to .08 0.2 to 0.9 0.3 to 1.0 0.3 to 1.0	Age, parity, use of HRT, menopause, country	Invasive ovarian cancer	1
		0 to 9 yr 10 to 14 yr 15 to 19 yr 20+	0.5 0.7 0.6 0.5	0.3 to 0.7 0.4 to 1.1 0.45 to 0.9 0.3 to 0.9		All ovarian cancers	1
		0 to 9 yr 10 to 14 yr 15 to 19 yr 20+	0.4 1.1 0.6 0.4	0.2 to 0.9 0.6 to 2.1 0.3 to 1.3 0.2 to 1.0		Borderline ovarian cancer	1
Hannaford, 2007[37]	Exposed: 744,000 person-years Unexposed: 339,000 person-years	Current and <60 mo 61 to 120 mo 121 to 180 mo 181 to 240 mo 241+ mo	0.5 0.42 0.28 0.79 0.61	0.24 to 1.01 0.18 to 0.97 0.11 to 0.71 0.38 to 1.67 0.24 to 1.52	Age, parity, smoking, social class, HRT use	Main dataset	1

Table 10. Data for outcomes on time since last OC use (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons (Time Since Last Use)	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Cohort (continued)							
Tworoger, 2007[154]	Exposed: 41,125 women years Unexposed: 54,027 women years	Current to <5 yr >5 yr to 10 yr >10 to 15 yr >15 to 20 yr >20 to 25 yr >25 to 30 yr >30 yr	1.05 0.53 0.9 0.88 1.15 1.24 1.13	0.60 to 1.83 0.30 to 0.94 0.61 to 1.33 0.61 to 1.27 0.81 to 1.63 0.86 to 1.80 0.71 to 1.80	Age, BMI, parity, BTL, smoking, age at menarche, age at menopause, duration of HRT use		1
Dorjgochoo 2009[88]	Exposed: 12,957 Unexposed: 15,557	Last used <19 yr ago Last used 19+ yr ago	0.99 1.21	0.48 to 2.01 0.64 to 2.29	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods		2

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; HRT = hormone replacement therapy; IUD = intrauterine device; mo = month/months; NR=not reported; OC = oral contraceptive; OR = odds ratio; yr=year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR=1.0.

[c]Meta-analysis code: 1=Included in this meta-analysis; 2=Excluded due to study used fewer than three comparisons; 3=Excluded due to categories presented are not amenable to combined analysis; 4=Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward; 5=Excluded due to grouping with another included article from the same study also reporting duration data.

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Table 11 lists the odds ratios for the meta-analysis of time since last OC use. The individual odds ratios show no evidence of a relationship as a function of time since last use. However, a test for differences between the four odds ratios gives a chi-square of 14.0 for 3 degrees of freedom, p=0.002.

Table 11. Estimated odds ratios by time since last OC use (ovarian cancer incidence)

Time Interval	Odds Ratio (95% Confidence Interval)	P-value
0–10 years	0.41 (0.34 to 0.50)	<0.0001
10–20 years	0.65 (0.56 to 0.74)	<0.0001
20–30 years	0.92 (0.76 to 1.12)	0.3692
>30 years	0.79 (0.58 to 1.12)	0.1036

We then ran an analysis using the midpoint of each interval as the estimate of the time for each subgroup. This resulted in the following model:

$$OR = Exp(-8729 + 0.0217 * years)$$

The slope was highly significant (p=0.0013). There is significant heterogeneity. The estimated value of σ is 0.25. The t-value is 4.81 for 8 degrees of freedom, p<0.0013. The value of σ is larger than many of the standard errors for the observed odds ratios.

Pooled Analyses

Among the three pooled analyses that reported time since last OC use, one study[21] reported that the relative risk of developing ovarian cancer was lower with more recent OC use. Women who had used OCs less than 10 years previously had a 29-percent decline in the risk of ovarian cancer for every 5 years of OC use, while those who last used OCs 20 to 29 years previously had a 15-percent reduction in risk. A second study[23] reported on the time since last OC use but found no clear trend in ovarian cancer risk, while a third study[24] found that risk reduction associated with OC use persisted regardless of the time elapsed since last use.

Sensitivity Analyses

We repeated our analyses excluding the five studies without patients from the United States. The estimates for the remaining four studies, three case-control and one cohort, were 0.40 (95% CI, 0.26 to 0.62 for use within the last 10 years, 0.66 (CI, 0.45 to 0.98) for use 10 to 20 years ago, 0.95 (CI, 0.58 to 1.56) for use 20 to 30 years ago, and 0.83 (CI, 0.46 to 1.50) for use >30 years ago.

We also performed analyses for studies published from 1990 forward (12 studies, 8 case-control and 4 cohort). The estimates were 0.45 (95% CI, 0.37 to 0.56 for use within the last 10 years, 0.70 (CI, 0.57 to 0.86) for use 10 to 20 years ago, 0.85 (CI, 0.63 to 1.14) for use 20 to 30 years ago and 0.88 (CI, 0.61 to 1.27) for use >30 years ago.

OC Formulations

Estrogen

Six studies[29,113,125,130,141,143] were included in this meta-analysis examining the effect of estrogen formulation on ovarian cancer incidence. All were case-control studies, and represented 2607 cases and 6400 controls. Five studies were rated good quality and one fair quality. We excluded one cohort study from the analysis[110] that did not contain dose information (Table 12).

The definition of a low-estrogen OC formulation varied among the six studies included in the meta-analysis, with three studies using a cutoff of 35 mcg estradiol,[29,113,130] two studies using a cutoff of 50 mcg estradiol,[125,143] and one study[141] reporting results for three separate doses of estradiol (20–34 mcg, 35–44 mcg, and ≥45 mcg).

Five studies[113,125,130,141,143] calculated odds ratios separately for high-dose or low-dose estrogen-containing OCs compared with never use. Of these, two studies[125,130] presented estrogen dose results stratified by low or high progestin dose.

Table 12. Data for outcomes on OC formulation (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Rosenblatt, 1992[140]	Cases: 393 Controls: 2561	High dose Low dose	0.68 0.81	0.44 to 1.05 0.051 to 1.29	Age, parity, center, year of diagnosis		4
Rosenberg, 1994[137]	Cases: 441 Controls: 2065	Norethindrone Norethindrone acetate Norethynodrel Ethynodiol diacetate Norgestrel Any mestranol >50mcg mestranol 50mcg mestranol Any ethinyl estradiol ≥50mcg ethinyl estradiol	0.5 0.7 0.9 1.3 0.2 0.6 0.9 0.7 0.5 0.4	0.3 to 0.9 0.2 to 3.2 0.2 to 3.2 0.5 to 3.1 0.1 to 0.7 0.4 to 1.0 0.5 to 1.8 0.2 to 2.0 0.2 to 1.0 0.1 to 1.0	Age, race, parity, family history, hysterectomy, removal of one ovary, geographic area, interview year	Formulation data refer only to use for >3 yr	4
Beard, 2000[83]	Cases: 103 Controls: 103	Any oral OC (as reported above) Substantial OC Any steroidal estrogen Substantial steroidal estrogen Any nonsteroidal estrogen Any progesterone Substantial progesterone	1.1 0.8 0.9 1.0 0.5 1.2 4.0	0.6 to 2.3 0.4 to 1.7 0.5 to 1.7 0.4 to 2.3 0.2 to 0.9 0.5 to 2.8 0.4 to 36	Crude		3
Ness, 2000[125]	Cases: 767 Controls: 1367	High estrogen/high progestin High estrogen/low progestin Low estrogen/high progestin Low estrogen/low progestin	0.5 0.7 0.6 0.5	0.3 to 0.7 0.3 to 1.8 0.3 to 1.3 0.3 to 0.6	Age, race, family history, number of pregnancies		1, 2
	Cases: 616 Controls: 1367	High estrogen/high progestin Low estrogen/low progestin	1.0 1.2	Reference 0.8 to 1.9	Age, race, family history, number of pregnancies	Invasive ovarian cancer N=616	1, 2
	Cases: 151 Controls: 1367	High estrogen/high progestin Low estrogen/low progestin	1.0 0.7	Reference 0.3 to 1.3	Age, race, family history, number of pregnancies	Borderline ovarian cancer N=151	1, 2
Sanderson, 2000[143]	Cases: 276 Controls: 388	Low dose estrogen Low and high dose estrogen High dose estrogen Unknown	0.6 0.6 0.8 0.9	0.3 to 1.1 0.3 to 1.3 0.5 to 1.2 0.6 to 1.5	Age, parity		1

Table 12. Data for outcomes on OC formulation (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Royar, 2001[141]	Cases: 282 Controls: 533	Low dose ≤35mcg ethinyl estradiol High dose >35mcg ethinyl estradiol Different formulations Avg daily ethinyl estradiol 20 to 34mcg Avg daily ethinyl estradiol 35 to 44 mcg Avg daily ethinyl estradiol 45 mcg or more No ethinyl estradiol or unknown ethinyl estradiol	0.20 0.65 0.46 0.14 0.33 0.57 0.55	0.08 to 0.47 0.40 to 1.05 0.30 to 0.71 0.06 to 0.36 0.15 to 0.72 0.36 to 0.90 0.34 to 0.89	Parity, family history, breastfeeding, tubal ligation, hysterectomy		1
Schildkraut, 2002[29]	Cases: 390 Controls: 2865	High estrogen Low estrogen Nonuser	1.0 .07 2.0	Reference 0.4 to 1.2 1.5 to 2.7			1, 2
	Cases: 390 Controls: 2865	High progesterone Low progesterone Nonuser	1.0 2.2 3.0	Reference 1.3 to 3.9 1.9 to 4.7	Age, parity, duration in months of use, latency, estrogen level		1, 2
	Cases: 390 Controls: 2865	High/high High/low Low/high Low/low Nonusers	1.0 0.0 2.1 1.6 2.9	Reference 0.0 to not estimable 1.2 to 3.7 0.9 to 3.0 1.8 to 4.5	Age, parity, latency, duration of use in months		1, 2
Pike, 2004[130]	Cases: 147 Controls: 304	High estrogen + high progestin High estrogen + low progestin Low estrogen + high progestin Low estrogen + low progestin Unknown	0.88 0.94 0.66 0.95 0.96	0.81 to 0.97 0.88 to 1.0 0.36 to 1.21 0.92 to 0.99 0.90 to 1.02	Age, race, parity, menopausal status, BMI, family history, SES, education, age at last birth, gravidity, OC use		1, 2

Table 12. Data for outcomes on OC formulation (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Lurie, 2007[113]	Cases: 745 Controls: 943	Any estrogen and high progestin Any estrogen and low progestin Various potency Never use High estrogen and any progestin Low estrogen and any progestin Various potency	0.54 0.41 0.22 1.00 0.61 0.33 0.45	0.38 to 0.75 0.18 to 0.94 0.12 to 0.41 Reference 0.42 to 0.89 0.21 to 0.52 0.24 to 0.85	Age, race, menopausal status, family history, center, education, gravidity, age at last pregnancy, tubal ligation, type of menopause, age at menopause, use of menopausal hormones, duration of OC use, time since first OC use		1, 2
	Cases: 745 Controls: 943	High estrogen and high progestin High estrogen and low progestin Low estrogen and high progestin Low estrogen and low progestin Various potencies	0.62 0.55 0.45 0.19 0.26	0.43 to 0.92 0.19 to 1.59 0.28 to 0.72 0.05 to 0.75 0.15 to 0.44	Age, race, menopausal status, center, education, gravidity, age at last pregnancy, tubal ligation, type of menopause, use of menopausal hormones, duration of OC use, time since first OC use		1, 2
Cohort							
Kumle, 2004[110]	Exposed: 75,533 Unexposed: 28,019	Progestin only Combination OCs Progestin only and combination OCs	0.3 0.5 0.7	0.1 to 1.1 0.3 to 0.8 0.4 to 1.0	Age, parity, menopausal status, HRT, country	Invasive ovarian cancer	3
		Progestin only Combination OCs Progestin only and combination OCs	0.5 0.5 0.7	0.2 to 1.2 0.4 to 0.7 0.5 to 1.0	Age, parity, menopausal status, HRT, country	All	3
		Progestin only Combination OCs Progestin only and combination OCs	1.0 0.6 0.9	0.4 to 2.9 0.3 to 1.0 0.5 to 1.5	Age, parity, menopausal status, HRT, country	Borderline ovarian cancer	3

Avg = average; BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; EE = ethinyl estradiol; HRT = hormone replacement therapy; IUD = intrauterine device; NR=not reported; OC = oral contraceptive; OR = odds ratio; yr=year/years

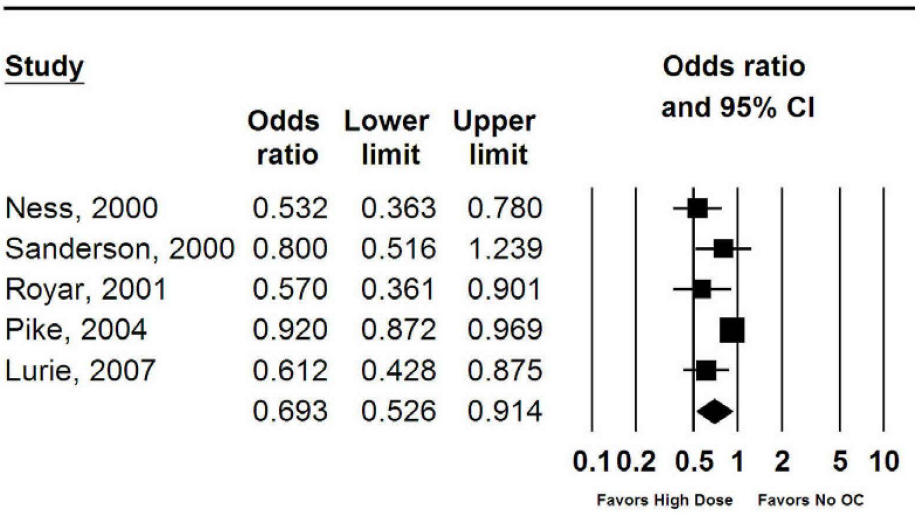
[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR=1.0.

[c]Meta-analysis code: 1=Included in estrogen formulation meta-analysis; 2=Included in progestin formulation meta-analysis; 3=Excluded due to study contained no dose information; 4=Excluded in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

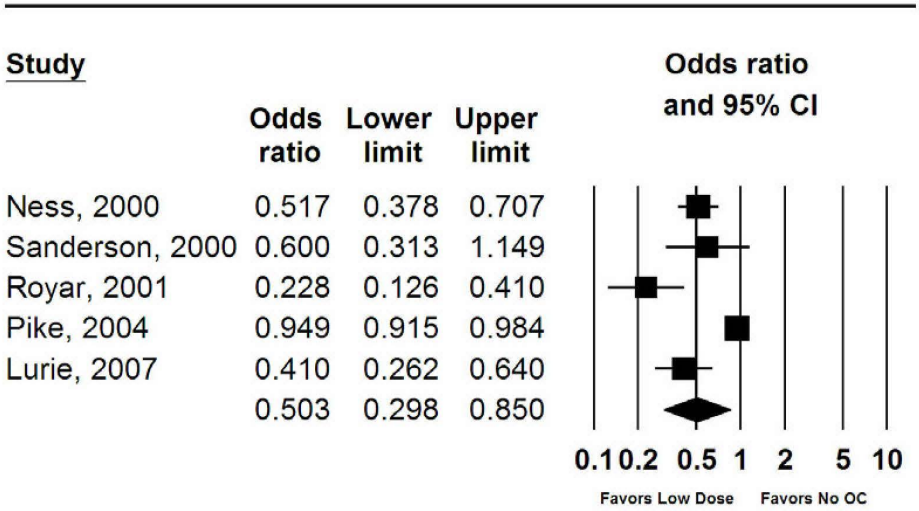
Figures 13 to 15 show the odds ratios for the meta-analyses on estrogen formulation. Compared with never use, the odds ratio for high-dose estrogen-containing OCs was 0.69 (95% CI, 0.53 to 0.91) (Figure 13). There was significant heterogeneity, with a Q-value of 16.44 for 4 degrees of freedom, p=0.002. Compared with never use, the odds ratio for low-dose estrogen-containing OCs was 0.50 (CI, 0.30 to 0.85) (Figure 14). There was significant heterogeneity, with a Q-value of 51.243 for 3 degrees of freedom, p≤0.001. One additional study calculated a direct odds ratio comparing high-dose to low-dose estrogen OC use.[29] When this was combined with the other five included studies, the odds ratio was 1.25 (CI, 0.95 to 1.64) (Figure 15). These results do not suggest a relationship between estrogen dose and ovarian cancer incidence. There was some evidence of heterogeneity, with a Q-value of 10.611 for 5 degrees of freedom, p=0.06.

Figure 13. Forest plot for high-dose estrogen (ovarian cancer incidence)



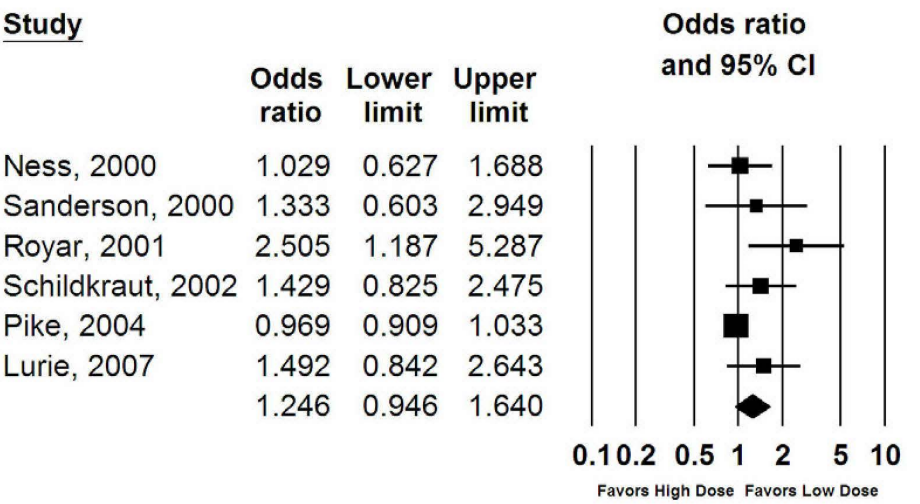
CI = confidence interval; OC = oral contraceptive

Figure 14. Forest plot for low-dose estrogen (ovarian cancer incidence)



CI = confidence interval; OC = oral contraceptive

Figure 15. Forest plot for high-dose versus low-dose estrogen (ovarian cancer incidence)



CI = confidence interval

Sensitivity Analyses

Analyses were repeated excluding one case-control study that was not performed within the United States. After this exclusion, a meta-analysis of the remaining five case-control studies revealed an odds ratio for high-dose estrogen-containing OC use of 0.69 (95% CI, 0.53 to 0.91), and for low-dose estrogen-containing OC use, an odds ratio of 0.60 (CI, 0.37 to 0.98). The odds ratio comparing high-dose with low-dose estrogen-containing OCs was 1.04 (CI, 0.90 to 1.21).

We also conducted analyses of studies published from 1990 forward (eight case-control studies). The odds ratio for high-dose estrogen-containing OC use was 0.68 (95% CI, 0.53 to 0.87), and for low-dose estrogen-containing OC use, an odds ratio of 0.55 (CI, 0.37 to 0.83). The odds ratio comparing high-dose to low-dose estrogen-containing OCs was 1.19 (CI, 0.93 to 1.51).

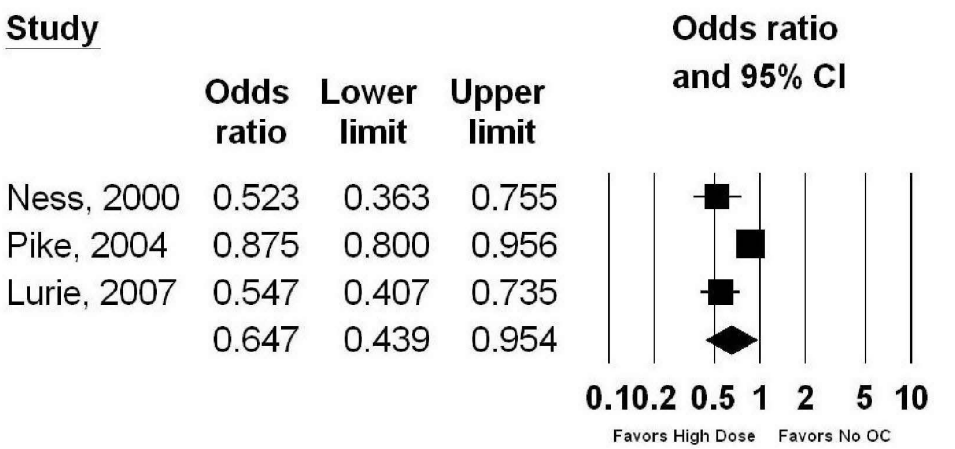
Progestin

Four studies[29,113,125,130] were included in this meta-analysis examining the effect of progestin formulation on ovarian cancer incidence (Table 12). Of these, all four were case-control studies representing 2049 cases and 5479 controls. All four studies were rated good quality. We excluded data from this analysis from reports that did not use progesterone-dosing terminology that facilitated a combined analysis.

The four included studies classified progesterone potency based on a subnuclear vacuolation assay and a delay of menses test. These methods have previously been described by Dickey and Stone,[163] who classified low-dose progestin OCs as those containing a relative potency cutoff of 0.2 mg norgestrel or less. Three studies stratified progestin results based on low or high estrogen dose.[113,125,130]

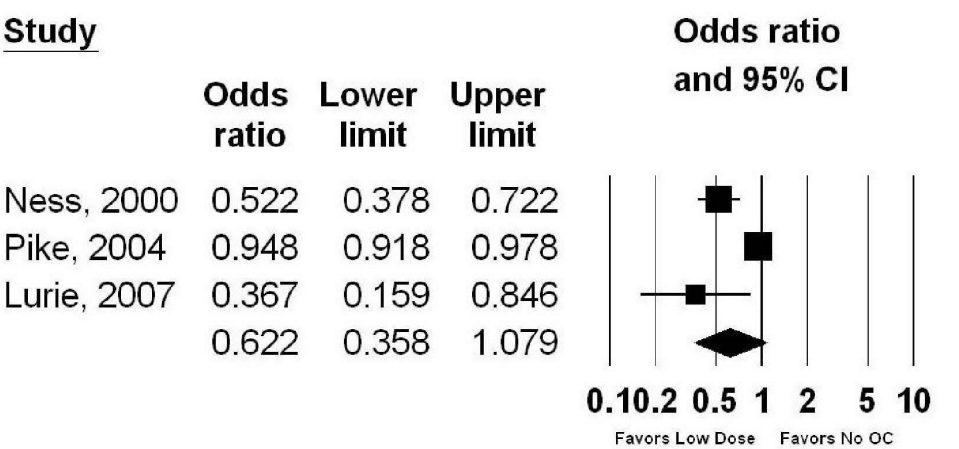
Figures 16 to18 show the odds ratios for the meta-analyses on progestin formulation. The odds ratio was 0.65 (95% CI, 0.44 to 0.95) for the three case-control studies of ovarian cancer incidence as a function of high-dose progestin (Figure 16). There was significant heterogeneity, with a Q-value of 14.97 for 2 degrees of freedom, p=0.001. The odds ratio was 0.62 (CI, 0.36 to 1.08) for the case-control studies of ovarian cancer incidence as a function of low-dose progestin (Figure 17). There was significant heterogeneity, with a Q-value of 17.80 for 2 degrees of freedom, p<0.001. One additional study calculated a direct odds ratio comparing high-dose with low-dose progestin OC use[29] (Figure 18). The random-effects meta-analysis of all four case-control studies reveals an odds ratio of 0.86 (CI, 0.60 to 1.21) for ovarian cancer incidence as a function of the ratio of high-dose progestin to low-dose. These results do not support a relationship between OC progestin dose and ovarian cancer incidence. There was some evidence of heterogeneity, with a Q-value of 7.52 for 3 degrees of freedom, p=0.057.

Figure 16. Forest plot for high-dose progestin (ovarian cancer incidence)



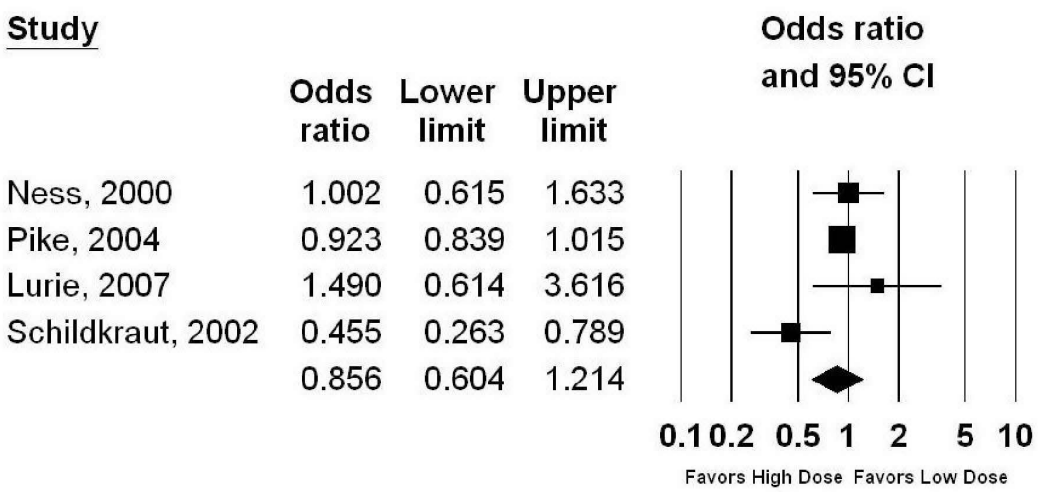
CI = confidence interval; OC = oral contraceptive

Figure 17. Forest plot for low-dose progestin (ovarian cancer incidence)



CI = confidence interval; OC = oral contraceptive

Figure 18. Forest plot for high- versus low-dose progestin (ovarian cancer incidence)



CI = confidence interval

Sensitivity Analyses

There were no poor-quality studies performed outside of the United States or studies published before 2000 addressing progestin dose. Therefore, sensitivity analyses were not performed.

Special Populations

BRCA Mutation Carriers

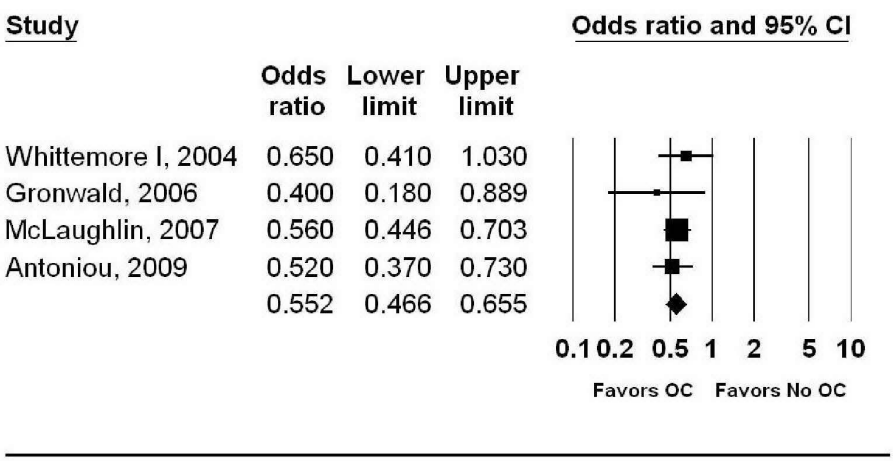
Four studies[81,94,116,159] were included in the meta-analyses examining the relationship between carriers of BRCA1 and BRCA2 genetic mutations and ovarian cancer incidence. Of these, three were case-control studies representing 1096 cases and 2878 controls and 1 cohort study representing 3181 participants. One study was rated good quality and three fair quality (Table 5).

Data were available to compare affected and unaffected BRCA1 mutation carriers; affected and unaffected BRCA2 mutation carriers; and a combined group of affected and unaffected BRCA1 or BRCA2 carriers. We excluded studies[115,118] from the analyses that compared mutation carriers with ovarian cancer to control groups who were predominantly noncarriers or who were not tested for BRCA1 or BRCA2.

Figures 19 to 21 show the odds ratios for the meta-analyses on BRCA1 mutation carriers. The odds ratio was 0.55 (95% CI, 0.47 to 0.66) for the four studies of ovarian cancer incidence in patients with the BRCA1 gene as a function of OC use (Figure 19). There was no significant heterogeneity, with a Q-value of 1.24 for 3 degrees of freedom, p=0.743. The odds ratio was 0.65 (CI, 0.34 to 1.24) for the three studies of ovarian cancer incidence in patients with the BRCA2 gene as a function of OC use (Figure 20). There was no significant heterogeneity, with a Q-value of 4.68 for 2 degrees of freedom, p=0.096. The odds ratio was 0.58 (CI, 0.46 to 0.73) for the three studies of ovarian cancer incidence that combined women with either the BRCA1 gene or BRCA2 gene (Figure 21). There was no significant heterogeneity, with a Q-value of 3.12 for 2

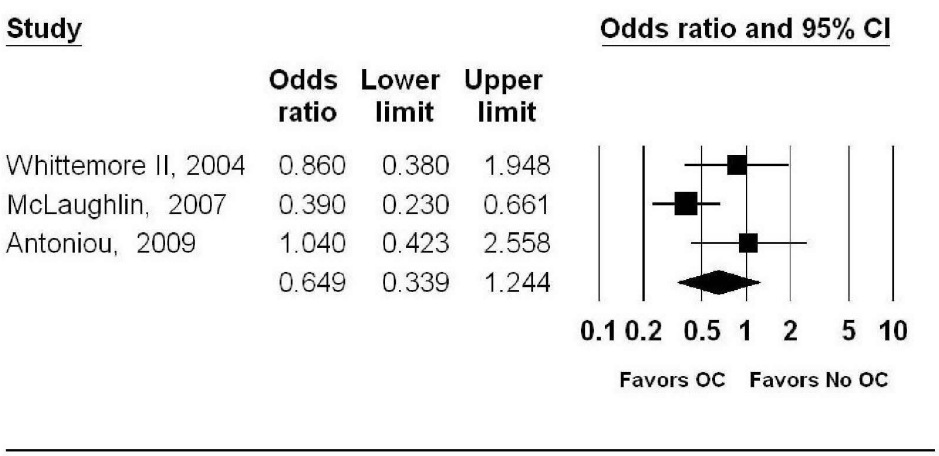
degrees of freedom, p=0.210. These analyses suggest that OCs reduce ovarian cancer incidence in all three gene categories. The odds ratios for the three groups were quite similar, and a test for a difference results in a p-value of 0.975.

Figure 19. Forest plot for BRCA1 carriers (ovarian cancer incidence)



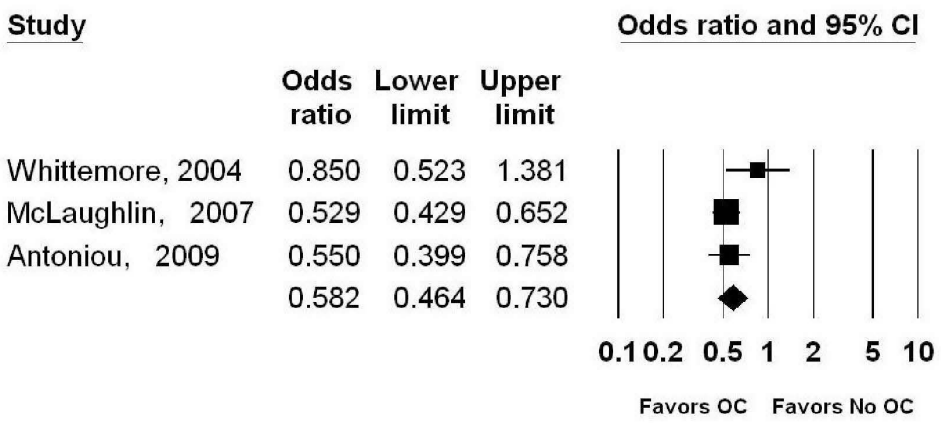
CI = confidence interval; OC = oral contraceptive

Figure 20. Forest plot for BRCA2 carriers (ovarian cancer incidence)



CI = confidence interval; OC = oral contraceptive

Figure 21. Forest plot for BRCA1 or BRCA2 carriers (ovarian cancer incidence)



CI = confidence interval; OC = oral contraceptive

Sensitivity Analyses

Analyses were repeated for the combined group of BRCA1 or BRCA2 mutation carriers including one additional study published in 1998. The odds ratio was 0.56 (CI, 0.45 to 0.69).

Sensitivity analyses were not done for study quality because no studies were rated as poor quality, and none were done comparing U.S. with non-U.S. studies because excluding non-U.S. studies left only two studies.

Family History of Ovarian Cancer

Three studies[87,149,158] were identified that examined the effect of family history on ovarian cancer incidence. All three were case-control studies: one was rated good quality and two fair quality. We excluded one pooled analysis[23] because it included some of the individual studies that were identified (Table 13).

Among these studies, two different definitions of a positive family history were used: (1) breast or ovarian cancer in a first-degree relative,[87,149] and (2) history of ovarian cancer in a sister or mother.[158] The studies also used two different categorizations of the referent group for OC use: (1) no OC use[149,158] or (2) use for less than 60 months.[87] The lack of consistency across studies precluded performing a meaningful meta-analysis by family history subgroups.

Table 13. Data for outcomes on family history (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control							
Gross, 1992[95]	With family history Cases: 31 Controls: 99	Never use 3 to 11 mo 12 to 24 mo 25 to 36 mo 37 to 60 mo ≥61 mo	1.0 3.1 1.7 1.5 1.1 0.3		Age, parity	Family history of ovarian cancer in mother, grandmother, sister, daughter or aunt	2
	No family history Cases: 225 Controls: 2351	Never use 3 to 11 mo 12 to 24 mo 25 to 36 mo 37 to 60 mo ≥61 mo	1.0 0.6 0.6 0.7 0.7 0.3		Age, parity	No family history	2
Godard, 1998[89]	Familial Cases Cases: 51 Controls: 152	Age at last OC use Never use 17 to 25 yr 25 to 35 yr 35 to 43 yr	 1.0 0.99 0.26 0.17	 Reference 0.28 to 3.51 0.08 to 0.79 0.036 to 0.83	Age at menarche, age at diagnosis, age at last childbirth, tubal ligation or hysterectomy, talc use, alcohol use	Family history of ≥1 person with breast cancer diagnosed <55 years or ovarian cancer	2
	Sporadic Cases Cases: 101 Controls: 152	Age at last OC use Never use 17 to 25 yr 25 to 35 yr 35 to 43 yr	 1.0 0.84 0.25 0.25	 Reference 0.28 to 2.55 0.10 to 0.62 0.10 to 0.64	Age at menarche, age at diagnosis, age at last childbirth, tubal ligation or hysterectomy, talc use, alcohol use	No family history	2
Tavani, 2000[149]	With family history Cases: 93 Controls: 139	Ever use Never use	1 1.4	Reference 0.4 to 4.4	Age, area of residence	Family history of breast and/or ovarian cancer in first-degree relatives	2
	No family history Cases: 878 Controls: 2619	Ever use Never use	1 1.2	Reference 0.9 to 1.7	Age, area of residence	No family history	2

Table 13. Data for outcomes on family history (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Chiaffarino, 2001[87]	With family history Cases: 129 Controls: 120	Never used or <60 mo ≥60 mo	1 1.0	Reference 0.2 to 4.2	Age, parity, family history, center, education	Family history of breast and/or ovarian cancer in first degree relatives	2
	No family history Cases: 901 Controls: 2286	Never used or <60 mo ≥60 mo	1 0.5	Reference 0.2 to 0.9	Age, parity, family history, center, education	No family history	2
Walker, 2002[158]	With family history Cases: 33 Controls: 24	≤48 mo use 49+ mo use Never use	0.34 0.07 1	0.08 to 1.55 0.01 to 0.44 Reference	Age, race, parity, tubal ligation	Family history of ovarian cancer in first-degree relative	2
	No family history Cases: 692 Controls: 1279	≤48 mo 49+ mo Never OC use	0.72 0.51 1	0.59 to 0.88 0.40 to 0.65 Reference	Age, race, parity, tubal ligation	No family history	2

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; HRT = hormone replacement therapy; IUD = intrauterine device; mo = month/months; NR = not reported; OC = oral contraceptive; OR = odds ratio; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR = 1.0.

[c]Meta-analysis code: 2 = Meta-analysis was not performed due to differences in definitions of positive family history and nonusers of OCs.

00803346

Parity and Gravidity

Two studies[123,126] were identified that examined the effect of gravidity on ovarian cancer incidence (Table 14). Both were case-control studies; in total they represented 1595 cases and 3137 controls. Both studies were rated good quality. When determining possible meta-analysis, we excluded one set of data from consideration[92] due to representation of that data in another included report and therefore did not have sufficient studies to warrant a formal meta-analysis.

Among nulliparous women, one study reported a significantly reduced risk of ovarian cancer among OC users (OR 0.43; 95% CI, 0.28 to 0.66),[123] and the other found no difference (OR 0.98; CI, 0.65 to 1.49).[126] Both studies reported a significantly reduced risk of ovarian cancer among parous women who were OC users (OR 0.72; CI, 0.61 to 0.85[123] and OR 0.68; CI, 0.56 to 0.83).[126] The odds ratios comparing gravidity 0 to gravidity 1+ were 0.60 (CI, 0.38 to 0.94)[123] and 1.44 (CI, 0.91 to 2.27).[126]

Table 14. Data for outcomes on parity/gravidity (ovarian cancer incidence)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control							
Parazzini, 1991[128]	Parity=0 Cases: 137 Controls: 273	Never Ever	1.0 0.6	Reference 0.3 to 1.3	Age	Nulliparous women	4
	Parity=1-2 Cases: 266 Controls: 795	Never Ever	1.0 0.5	Reference 0.3 to 0.9	Age	Women with parity 1-2	4
	Parity≥3 Cases: 102 Controls: 307	Never Ever	1.0 0.8	Reference 0.3 to 1.7	Age	Women with parity ≥3	4
Thomas, 1991[150]	Parity=0 Not reported	Never Ever	1.0 0.16	Reference 0.05 to 0.54		Nulliparous women	4
	Parity ≥1 Not reported	Never Ever	1.0 0.85	Reference 0.63 to 1.16		Women with parity ≥1	4
Ness, 2001[126]	Gravidity=0 Cases: 137 Controls: 119	Never OCs for contraception OCs for noncontraception OCs for both	1.0 0.9 1.3 0.9	Reference 0.5 to 1.7 0.6 to 3.2 0.4 to 1.8	Age, race, family history		1
	Gravidity=1 Cases: 107 Controls: 140	Never OCs for contraception OCs for noncontraception OCs for both	1.0 0.6 0.5 0.9	Reference 0.3 to 1.1 0.2 to 1.7 0.4 to 2.1	Age, race, family history		1
	Gravidity=2 Cases: 177 Controls: 346	Never OCs for contraception OCs for noncontraception OCs for both	1.0 0.6 0.7 1.0	Reference 0.4 to 1.0 0.3 to 1.6 0.5 to 2.0	Age, race, family history		1
	Gravidity≥3 Cases: 306 Controls: 754	Never OCs for contraception OCs for noncontraception OCs for both	1.0 0.7 0.9 0.5	Reference 0.5 to 1.0 0.5 to 1.6 0.3 to 0.9	Age, race, family history		1

Table 14. Data for outcomes on parity/gravidity (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Case-Control (continued)							
Greer, 2005[92]	Parous women Cases: 715 Controls: 1631	Never Single episode; 1 to 6 mo Single episode; 7 to 12 mo Single episode; ≥13 mo ≥1 episode; 1 to 6 mo ≥1 episode; 7 to 12 mo ≥1 episode; ≥13 mo	1.00 0.71 1.04 0.66 0.71 0.97 0.62	Reference 0.50 to 0.99 0.66 to 1.63 0.48 to 0.90 0.51 to 0.99 0.64 to 1.47 0.48 to 0.81	Age		2
	Nulliparous women Cases: 216 Controls: 168	Never user Single episode; 1 to 6 mo Single episode; 7 to 12 mo Single episode; ≥13 mo ≥1 episode; 1 to 6 mo ≥1 episode; 7 to 12 mo ≥1 episode; ≥13 mo	1.00 1.04 1.08 0.84 1.05 1.08 0.68	Reference 0.52 to 2.08 0.42 to 2.78 0.46 to 1.56 0.55 to 2.01 0.49 to 2.34 0.42 to 1.11	Age		2
Ness, 2011[123]	Gravidity=0 Cases: 134 Controls: 143	Never OCs for contraception OCs for noncontraception OCs for both	1.00 0.46 0.61 0.31	Reference 0.25 to 0.86 0.25 to 1.52 0.15 to 0.67	Age, race, family history, infertility		1
	Gravidity=1 Cases: 114 Controls: 188	Never OCs for contraception OCs for noncontraception OCs for both	1.00 0.99 0.60 0.99	Reference 0.58 to 2.02 0.44 to 2.23 0.22 to 1.69	Age, race, family history, infertility		1
	Gravidity=2 Cases: 216 Controls: 458	Never OCs for contraception OCs for noncontraception OCs for both	1.00 0.51 0.89 0.50	Reference 0.34 to 0.77 0.40 to 1.99 0.28 to 0.88	Age, race, family history, infertility		1
	Gravidity≥3 Cases: 404 Controls: 989	Never OCs for contraception OCs for noncontraception OCs for both	1.00 0.85 0.77 0.70	Reference 0.64 to 1.14 0.45 to 1.32 0.45 to 1.09	Age, race, family history, infertility		1

Table 14. Data for outcomes on parity/gravidity (ovarian cancer incidence) (continued)

Study[a]	Sample Size	Comparisons	OR[b]	95% CI[b]	Covariates	Special Population (if Applicable)	Meta-Analysis Code[c]
Pooled							
Hartge, 1994[104]	Parity>=3 Cases: 333 Controls: 2466	No OC OCs for 1-3 yr OCs for ≥4 yr	1.0 1.8 2.2	Reference 1.2 to 2.7 1.6 to 3.2	Tubal ligation, hysterectomy		3
	Parity=1-2 Cases: 448 Controls:2029	No OC OCs for 1-3 yr OCs for ≥4 yr	1.5 2.6 3.7	0.95 to 2.3 1.7 to 3.9 2.6 to 5.4			3
	Parity=0 Cases:295 Control: 816	No OC OCs for 1-3 yr OCs for ≥4 yr	2.2 5.8 5.5	1.3 to 3.9 3.6 to 9.3 3.7 to 8.0			3

BMI = body mass index; BRCA = breast cancer genetic mutation; BSO = bilateral salpingo-oophorectomy; BTL = bilateral tubal ligation; CI = confidence interval; mo = month/months; OC = oral contraceptive; OR = odds ratio; NR = not reported; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Unless otherwise presented, never use is the reference category with an OR=1.0.

[c]Meta-analysis code: 1 = Study meets inclusion criteria for meta-analysis; 2 = Excluded from possible meta-analysis due to grouping with another included article also reporting results by gravidity; 3 = Excluded pooled analysis due to no other studies to combine it with; 4 = Excluded from possible meta-analysis in main analyses of studies from 2000 forward, included in sensitivity analyses of studies from 1990 forward.

00803350

Sensitivity Analyses

No sensitivity analyses were performed because there were too few studies.

OC Use and Ovarian Cancer Mortality

Three studies[33,164-167] were identified that examined the effect of OC use on ovarian cancer mortality. All three were cohort studies and were rated fair quality. Two of the included studies[33,165] were large, population-based cohort studies representing 46,112 subjects and 602,700 reported person-years and assessed death from ovarian cancer as a primary outcome among ever versus never OC users. Both of these studies reported a significant reduction in ovarian cancer mortality among OC users that was similar in magnitude and direction as the reduction in incidence discussed above. The third study[167] identified a cohort of women with ovarian cancer and subsequently compared survival outcomes between OC users (n=310) and nonusers (n=366), with nonsignificant findings (Table 15).

Table 15. Data for ovarian cancer mortality

Study[a]	Study Details	OR	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[b]
Cohort							
Survival After Diagnosis of Ovarian Cancer							
Nagle, 2008[167]	Cohort of women with ovarian cancer in three Australian states Exposed: 310 women Unexposed: 366 women	0.88	0.70 to 1.11	Stage, age group, histologic grade, residual disease, smoking	Australia/NZ	Fair	2
Population-Level Mortality							
Hannaford, 2010[33]	Royal College General Practitioners Oral Contraceptive Study Exposed: 28,806 women Unexposed: 17,306 women	0.53	0.38 to 0.72	Age, parity, smoking and social class	UK	Fair	2
Vessey, 2010[165]	Oxford Family Planning Association contraception study 602,700 person-years of observation for unexposed and exposed	0.87	0.79 to 0.96	Age, parity, social class, smoking, BMI	UK	Fair	2

CI = confidence interval; NZ = New Zealand; OC = oral contraceptive; OR = odds ratio; UK = United Kingdom

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Meta-analysis code: 2 = Excluded from the meta-analysis due to differences in study populations.

00803352

Strength of Evidence for OC Use and Risk of Ovarian Cancer

The strength of evidence for each outcome is described in Table 16 using the four domains listed as guidance. Because no randomized controlled trials were included in our analysis, the risk of bias was categorized as medium at best and high if other possible sources of bias were identified. With regard to directness of evidence, relationships between high and low steroid hormone doses and ovarian cancer incidence were considered to be indirect based on the use of "never OC use" as the reference category in those studies.

We graded as moderate the strength of evidence for relationships between ever OC use and ovarian cancer incidence and mortality in the general population and between ever OC use and ovarian cancer incidence in the BRCA mutation-carrying population. The relationship between duration of OC use and ovarian cancer incidence was also graded as moderate. The strength of evidence for the remaining relationships was graded as low.

Table 16. Strength of evidence domains for the effect of OC use on ovarian cancer

Comparison	Number of Studies (Women and/or Person-years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ovarian Cancer in Overall Population						
Ever vs. never use	24 (657,055 and 3,981,072 person-years)	Medium	Consistent	Direct	Precise	Moderate 0.73 (0.66 to 0.81)
Duration of use	15 (574,363 and 3,493,072 person-years)	Medium	Consistent	Direct	Precise	Moderate 1–12 mo: 0.91 (0.78 to 1.07) 13–60 mo: 0.77 (0.66 to 0.89) 61–120 mo: 0.65 (0.55 to 0.77) >120 mo: 0.43 (0.37 to 0.51)
Age at first use	6 (111,817)	High	Consistent	Direct	Imprecise	Low <20 yr: 0.63 (0.45 to 0.89) 20–24 yr: 0.71 (0.51 to 0.99) 25–30 yr: 0.67 (0.46 to 0.99) > 30 yr: 0.89 (0.60 to 1.32)
Time since last use	8 (210,069 and 1,083,000 person-years)	High	Inconsistent	Direct	Imprecise	Low 0–10 yr: 0.41 (0.34 to 0.50) 10–20 yr: 0.65 (0.56 to 0.74) 20–30 yr: 0.92 (0.76 to 1.12) >30 yr: 0.79 (0.58 to 1.12)

Table 16. Strength of evidence domains for the effect of OC use on ovarian cancer (continued)

Comparison	Number of Studies (Women and/or Person-years)	Domains Pertaining to SOE				SOE and Magnitude of Effect (95% CI)
		Risk of Bias	Consistency	Directness	Precision	
Incidence of Ovarian Cancer in Overall Population (continued)						
High-dose vs. low-dose estrogen	6 (9007)	High	Consistent	Indirect	Imprecise	Low 1.25 (0.95 to 1.64)
High-dose vs. low-dose progestin	4 (7528)	High	Inconsistent	Indirect	Imprecise	Low 0.86 (0.60 to 1.21)
Incidence in BRCA1- or BRCA2-Positive Women						
Ever vs. never use	3 (6855)	Medium	Consistent	Direct	Precise	Moderate 0.58 (0.46 to 0.73)
Incidence in BRCA1-Positive Women						
Ever vs. never use	4 (5519)	Medium	Consistent	Direct	Precise	Moderate 0.55 (0.47 to 0.66)
Incidence in BRCA2-Positive Women						
Ever vs. never use	3 (1592)	Medium	Inconsistent	Direct	Imprecise	Low 0.65 (0.34 to 1.24)
Incidence in Women With Family History						
Ever vs. never use	3 (9193)	High	Inconsistent	Direct	Imprecise	Low Decreased incidence
Incidence in Gravid/Parous and Nulligravid/Nulliparous Women						
Ever vs. never use	2 (4732)	Medium	Inconsistent	Direct	Imprecise	Insufficient
Mortality From Ovarian Cancer						
Ever vs. never use	2 (46,112 and 602,700 person-years)	Medium	Consistent	Direct	Imprecise	Moderate Decreased cause-specific mortality
Survival Among Women With Ovarian Cancer						
Ever vs. never use	1 (676)	High	NA	Direct	Imprecise	Insufficient (not performed)

CI = confidence interval; mo = month/months; NA = not applicable; SOE = strength of evidence; yr = year/years

Discussion

In the systematic review and meta-analysis for Section 2, OC use was associated with a decreased incidence of ovarian cancer (OR 0.73, 95% CI, 0.66-0.81), with results from two large cohort studies showing a concomitant decrease in mortality. There is a positive relationship between the duration of OC use and the degree of the protective effect. These findings are consistent with prior pooled analyses,[21,23,24] which reported odds ratios for ever versus never OC use of between 0.60 and 0.73 and similarly identified a relationship between longer duration of OC use and lower incidence of ovarian cancer. We did not identify a significant relationship between time since last OC use and degree of protection—although such a relationship has been identified in the largest prior pooled analysis.[21] Note that we found no evidence for publication bias in any of the meta-analyses (Appendix E).

Temporal Relationships in OC Use

The results of our meta-analysis show a strong relationship between duration of OC use and the incidence of ovarian cancer (Figure 12). Women who use OCs for 10 or more years show a reduction in ovarian cancer incidence of more than 50 percent. Prior pooled analyses are consistent with these findings.[21,23,24] While our reported odds ratio comparing OC use for less than 12 months with never use does not meet criteria for statistical significance, our duration analysis suggests that there is no time threshold for OC effectiveness, and the duration-response relationship likely starts as soon as a woman commences OC use.

Regarding age at first OC use, the odds ratios also appear to show a clearly positive relationship. This suggests that the earlier a woman begins using OCs, the greater the reduction in ovarian cancer incidence. However, it is not possible to differentiate the effects of age at first use from the effects of duration of use. Our findings are consistent with the largest pooled analysis,[21] and are not unexpected, since the earlier a woman starts using OCs, the longer the potential duration of use. The number of studies (6) in our primary analysis of age at first OC use was much lower than the number of studies (15) in the analysis of duration, and so it is not possible to determine which factor is more predictive. The protective effect of OCs appears to attenuate with increasing time since last use, again consistent with the findings of the Collaborative Group,[21] although it remains significantly reduced even up to 30 years after stopping. Although the data available at the study level preclude estimation of the joint effect of duration and time since last use, stratified analysis of the pooled individual data by the Collaborative Group suggest that the magnitude of protection with increased duration is greater than the attenuation with time since last use.

Women at Elevated Genetic Risk for Ovarian Cancer

The results of our meta-analysis suggest that ever use of OCs reduces the risk of ovarian cancer in BRCA1 or BRCA2 mutation carriers similar to what has been observed consistently in the general population. The odds ratio for ever use of OCs (OR 0.58; 95% CI, 0.46 to 0.73) for BRCA1 or BRCA2 mutation carriers was lower than the odds ratio calculated from the overall meta-analysis (OR 0.73, 95% CI, 0.66 to 0.81).

Although the breast cancer literature clearly demonstrates that clinical and pathologic characteristics of BRCA1-associated cancers differ from BRCA2-associated cancers and sporadic cancers, the same does not appear to be true for ovarian cancer.[168] Our analyses of the effects of OCs in BRCA1 and BRCA2 mutation carriers found similar odds ratios for ovarian cancer in each group, and a test for differences between groups was not statistically significant ($p=0.916$). Although the analyses did not suggest there were statistically significant differences between BRCA1 and BRCA2 mutation carriers, these results should be interpreted cautiously because of the small number of studies and the relatively small sample sizes for BRCA2 mutation carriers.

For women that do not have a known BRCA1 or BRCA2 mutation but are at increased risk for ovarian cancer due to a family history of breast or ovarian cancer, the data were inadequate to perform a meta-analysis because of differences between studies in their definitions of family history and the reference group to which OC users were compared. Within individual studies, particularly those focusing specifically on a family history of ovarian cancer, the relatively small numbers within the strata defined by a positive family history led to unstable estimates. The possible use of OCs as an ovarian cancer prevention strategy is clearly of interest to women with

a family history of ovarian or breast cancer; however, the published data do not provide consistent evidence to support a recommendation for use.

Limitations

In an effort to enhance the applicability of these findings to contemporary OC formulations and dosages, we included only studies published on or after January 1, 2000, for the primary analysis and 1990 for the sensitivity analysis. However, our meta-analysis produced a very similar odds ratio comparing ever use with never use (0.73) to odds ratios reported in the sensitivity analysis (0.72) and a pooled analyses that included older studies. This suggests that current OC formulations may have a similar effectiveness to older formulations in reducing the incidence of ovarian cancer. This is supported by our finding that the relative estrogen and progestin doses in OCs do not appear to have an impact on ovarian cancer incidence. However, given that the age of peak incidence of ovarian cancer is in a woman's early 60s, even more recent publications do not capture the potential long-term effect of formulations introduced in the past 20 years.

Another limitation of the current analysis is the degree of generalizability of the included studies to clinical decisionmaking. The included studies almost never specifically reported the reasons for OC use. It is likely that most women who have taken OCs have done so for contraception or to control symptoms related to menses. Therefore, the use of OCs specifically to prevent ovarian cancer has not been addressed in reported studies, and use of the currently available data to guide a risk/benefit discussion regarding chemoprophylaxis is premature.

The main limitation of our analysis is the lack of any randomized, prospective trials examining the preventive effect of OCs on ovarian cancer, raising the potential for bias. The most common study design within our primary ever/never incidence analyses was case-control (71%), with a minority being cohort studies (29%); given that ovarian cancer is relatively uncommon, this is not unexpected. The point estimate for case-control studies (0.72) was lower than for cohort studies (0.75), suggesting that there may be some residual confounding in the case-control studies. Likewise, although the vast majority of studies were rated as good or fair quality (92%), there was marked inconsistency across studies, particularly in the methods for adjustment of confounding. Individual odds ratios or relative risks were always adjusted for potential confounders, but both the choice of covariates and the way the covariates were modeled in the reported results were not consistent among studies (Tables 5, 6, 8, 10, 12–15). For example, relevant ages and durations of exposure were described using a variety of categories with widely varying definitions.

The observed association between OC use and reduced ovarian cancer risk (and for many of the other associations discussed in Sections 3 and 4) fulfills many of the classic criteria for causal inference in epidemiology,[169] including strength of association, consistency across studies, temporality, a biological gradient, biological plausibility, and coherence. However, the potential for the limitations discussed above to lead to biased estimates of the effects of OC require considerable caution when using the results for clinical decisionmaking. Although the literature synthesis for each outcome and the model (described in Section 5) represent our best efforts at integrating the available data quantitatively, the inherent limitations of observational studies mean that we cannot rule out the possibility that some or all of the observed associations between OC use and both harmful and beneficial outcomes are the result of unmeasured confounding.

Future Research

The current literature consistently shows a statistically significant reduction in ovarian cancer risk among women with a history of OC uses, with greater reductions in risk with longer duration of use. Results were similar across different subgroups with varying degrees of risk, such as nulliparous women and BRCA1 and BRCA2 mutation carriers. While the overall body of evidence is supportive of the beneficial effects of OCs on ovarian cancer, the potential for unmeasured bias is substantial. Even if the magnitude of the observed protective association is accurate, our analysis demonstrates that there is insufficient evidence to guide more specific recommendations regarding the preferred OC formulation and dose, the optimal time period of use for ovarian cancer prevention, and the benefits in certain high-risk women. Ideally, many of these issues would be resolved by a randomized trial, but, as discussed in Section 5, the challenges to conducting such a trial may be insurmountable.

While the current analysis did not identify a relationship between estrogen or progestin formulation and incidence of ovarian cancer, there were a limited number of studies meeting criteria for these meta-analyses. In particular, the progestin component of the OC formulation appears to have an effect on the ovarian epithelium in animal studies.[170] Given that only four studies defined progestin dose uniformly and were included in the meta-analysis, further investigation into the relationship between progestin dose/formulation and ovarian cancer incidence is warranted. This is particularly important given that both the estrogen and progestin components are likely related to the risk of some of the adverse outcomes associated with OC use—especially acute vascular events (see Section 4).

Our analyses were based on more recently published data than previous pooled analyses were, yet we arrived at a similar estimate of the odds ratio associated with ever OC use. This suggests that lower dose OCs—which are more commonly evaluated in recent studies—are potentially as effective as higher dose OCs in reducing ovarian cancer risk. Continued evaluation of effects by dose of OCs is warranted, especially since some of the older women included in studies published since 1990 would have taken OCs when higher doses were more commonly prescribed.

Further research is needed to sort out the relative importance of the duration and timing of use of OCs. Greater reductions in risk were observed for women who were younger at first use of OCs; however, data were not available to determine whether this was due to longer duration of use among women who initiated OC use at younger ages. Analogously, although ovarian cancer risk was lower among more recent OC users compared with those with a longer time since last use, these analyses did not account for duration of use. Understanding the combined effects of timing and duration is particularly important for making recommendations to women of mid-to-late reproductive age who are considering OC use for ovarian cancer prevention but not necessarily for contraception. To facilitate future systematic reviews, one step would be to standardize the categories and descriptive statistics for reporting results. Although particular categorization choices may be best suited for analyzing individual studies on the basis of study design and characteristics of a given population, reporting of standardized results—perhaps as an appendix to the main analysis—would greatly improve the ability to combine published results in meta-analysis.

Additional research is also needed to learn whether women at high risk for ovarian cancer due to their family history show a similar benefit with OC use as women from the general population. The proportion of women with a reported family history of ovarian cancer is quite small in most studies; however, this group may be keenly interested in chemoprevention given

the high mortality of ovarian cancer. It would be highly desirable for pooled analyses to include a sufficient number of women with a positive family history to provide stable risk estimates.

Section 3. Oral Contraceptives and Other Cancers

Background

Nearly half (49%) of all pregnancies in the United States are unintended, with 19 percent considered unwanted pregnancies.[171] Oral contraceptives (OCs) are the most common form of effective and reversible contraception in the United States.[172] Use of OCs significantly decreases personal and societal burdens associated with unintended or unwanted pregnancy.[173,174] Additionally, OCs have significant noncontraceptive health benefits, such as improving acne or regulating dysmenorrhoea.[175-178] Using OCs, however, is not without risks. Numerous studies demonstrate serious complications associated with OC use including venous thromboembolic disease, myocardial infarction, and stroke.[179-181]

Use of OCs also may influence the risk of certain cancers.[56] OC use may promote or initiate tumors of the breast or cervix.[50,67,182] For breast cancer, these risks may be even greater for populations at elevated risk due to family history of cancer or genetic mutation carrier status (e.g., BRCA1/2); however, results from studies are inconclusive.[51,183] Moreover, the use of OCs has also been associated with a greater risk of certain clinically challenging types of breast tumors.[184] Conversely, OC use is associated with significant reductions in colorectal and endometrial cancers.[54,56] Our systematic review and meta-analyses support a significant risk reduction for ovarian cancer incidence and mortality associated with OC use (Section 2). However, assessment of the risk of cancer associated with OC use is fraught with difficulties. For example, cancer is a disease with a long latency period, and the time between exposure to OCs and diagnosis of cancer may span decades. Also, temporal variations in the OC formulations available on the market and used over a woman's lifetime may influence associations between cancer risk and OC use. Further, patterns of OC use over a lifetime may be influenced by factors that also affect cancer risks (e.g., gravidity, parity, breastfeeding). Last, duration of OC use or length of time since ceasing use (i.e., recency) may moderate the risk of cancers associated with OCs.[50,121]

In this section of our systematic review, we summarize the current data on associations between OC use and four common cancers among women—breast, cervical, colorectal, and endometrial. When possible, we conducted meta-analyses of the literature assessing the risk of cancer incidence and mortality associated with the use of OCs. We date-limited our search to studies published after 1999 to minimize the influence of OC formulations that are no longer available on the U.S. market and to increase generalizability to current clinical practice. When possible, we also examined associations by duration of OC use and time since last OC use on incidence of these cancers.

Relevant Key Questions

The seven KQs developed for the entire systematic review are listed in Section 1 (refer to Figure 7 for a roadmap of this report). For Section 3, we performed a systematic review and meta-analysis for the cancer outcomes described in two of the seven KQs that address the potential effect of OCs on the risk of developing other cancers (breast, cervical, colorectal, and endometrial):

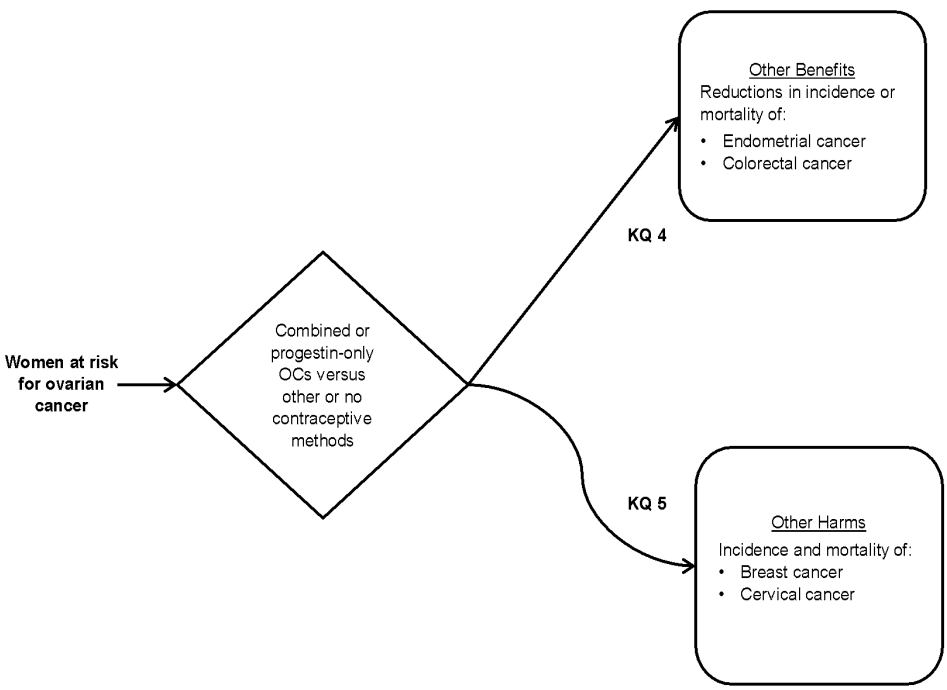
KQ 4: Aside from pregnancy prevention, are there other benefits of OC use in reducing the risks of endometrial cancer or colorectal cancer?

KQ 5: What are the harms of OC use, including breast cancer incidence, cervical cancer incidence, venous thromboembolic disease, stroke, or myocardial infarction? How do these harms vary by dose or formulation, duration of use, or specific population?

Analytic Framework

Figure 22 shows the analytic framework that guided this section of the review.

Figure 22. Analytic framework for OCs and other cancers



KQ = Key Question; OC = oral contraceptive

Methods

Inclusion and Exclusion by PICOTS

Table 17 describes the PICOTS criteria that guided the literature search for this section of the review.

Table 17. Summary of inclusion and exclusion criteria for OCs and other cancers

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• All KQs: ○ Women taking oral contraceptives (OCs) for contraception or women taking OCs for primary prevention of ovarian cancer[a] ○ Women who do not have a history of ovarian cancer and have not undergone bilateral oophorectomy	Nonhuman studies
Interventions	OC use (includes OC use for varying time periods and OC use with different formulations)	Study does not provide a description of at least one of the following: (1) OC formulation(s) used (2) Length of OC use
Comparators	No use of combination or progestin-only OCs, including either no contraceptive method at all or contraceptive methods other than combination or progestin-only OCs (e.g., natural family planning, barrier methods, sterilization, intrauterine devices, injectable or implantable hormonal contraception)	Study does not include controls; i.e., an estimate of outcomes in women not using OCs (population estimates are acceptable)
Outcomes	Study reports quantitative association between exposure to OCs and either incidence or disease-specific mortality for any of the following: • KQ 4: ○ Endometrial cancer ○ Colorectal cancer • KQ 5: ○ Breast cancer ○ Cervical cancer	Study only reports outcomes related to assisted reproductive technologies or abortion
Timing	Studies of any duration	None
Setting	All settings	None

Table 17. Summary of inclusion and exclusion criteria for OCs and other cancers (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Study design	• Controlled studies (randomized trials, cohort studies, case-control studies), pooled patient-level meta-analyses, or systematic reviews and study-level meta-analyses[b] • Study sample size ≥ 100 subjects for nonrandomized studies[c]	• Not a clinical study (e.g., editorial, non–systematic review, or letter to the editor) • Exploratory study with inadequate sample size
Publications	• English-language only • Peer-reviewed articles • Study reports a breast, endometrial, cervical, or colorectal cancer outcome of interest and was published on or after 01-Jan-2000[d]	Non-English articles[e]

KQ = Key Question; OC = oral contraceptive
[a]If the purpose of OC use was unclear, it was assumed to be contraception.
[b]Systematic reviews and study-level meta-analyses were excluded from direct abstraction; those representing key sources were hand-searched as potential sources of additional material.
[c]Small nonrandomized studies <100 subjects were excluded because confidence intervals for outcomes of interest are generally quite wide if appropriate adjustment for confounding is performed, and variability in reporting of potential confounders makes meta-analysis problematic.
[d]Date ranges for these cancer outcomes were selected to balance generalizability (OC formulations used in earlier studies not currently on market) and power (peak incidence of cancers 10 to 30 years after typical use of oral contraceptives).
[e]Non-English articles were excluded (1) due to the high volume of literature available in English-language publications (including the majority of known important studies) and (2) due to concerns about the applicability of non-English publication studies to populations in the United States. The variability in OC formulations approved for use across countries increases the likelihood that non-English language studies would include OCs not available or not in use in the United States.

Meta-Analytic Methods

To examine quantitatively the effect of OCs on the risk of breast, cervical, colorectal, or endometrial cancer, we performed meta-analyses on the following relationships when we had sufficient studies:

- Ever versus never OC use:
  - Ever versus never OC use among BRCA1 and BRCA2 genetic mutation carriers (breast cancer only)
- Temporal relationships:
  - Duration of OC use
  - Time since last OC use (breast cancer only)

We performed the meta-analyses using Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ; 2005).[68] Confidence intervals from the included study publications were entered into the Comprehensive Meta-Analysis (CMA) program. However, many of these confidence intervals had been rounded to a single decimal place. The CMA program checks the intervals for symmetry in the logarithmic scale. In certain cases, the rounded limits were not accepted by CMA. In such cases, we kept the point estimate as given but changed the confidence limits so that they were symmetric. This resulted in slight differences in the confidence intervals in the forest plots when compared with the study publications.

We excluded studies that were conducted in special populations, such as BRCA mutation carriers, women with family histories of cancer, or specific cancer subtypes. When studies only gave results by subgroup (premenopausal, postmenopausal), we combined subgroups only when the combined group represented the total study population. We estimated pooled odds ratios with 95% confidence intervals (95% CIs) using a random-effects model when study designs and

outcomes reported were similar. We evaluated heterogeneity visually and with the Cochran Q statistic using a threshold p-value of less than 0.10 to define significant heterogeneity. We stratified analyses by study type (case-control, cohort).

Pooled Analyses

We included pooled analyses in our meta-analyses if all three of the following conditions were met:

- None of the individual studies included in the pooled analysis had already been included for meta-analysis.
- At least half of the studies in the pooled analysis were published on or after January 1, 2000.
- Data in the pooled analyses were presented such that their inclusion in the current meta-analysis was feasible.

Ever Versus Never OC Use

For the ever versus never OC use meta-analysis, we excluded studies that reported effects for only a particular subpopulation (e.g., studies reporting odds ratios only for women with a BRCA mutation) but that did not report the effects for the general population. Studies that reported ever OC use odds ratios for two or more mutually exclusive subpopulations were included in the meta-analysis and results for the subpopulations were combined.

Temporal Relationships

Duration of OC Use

We used a random-effects model to compute odds ratios after determination that sufficient studies met criteria to perform a meta-analysis on the effect of duration of OC use. We required that the odds ratios were given relative to no OC use and that the population studied was not restricted to a particular special population. We assumed that each odds ratio, OR_{ij}, could be described by the following model:

$$Ln\left[OR_{ij}\right]=\alpha_i+\sum_{j=1}^{k} x_{ij}\,\beta_j,$$

where i denotes the study, j denotes the specific time interval, and k is the number of time intervals used in the model. The α_i are assumed to be random and normal with mean 0 and variance $(SE_{ij}^2 + \sigma^2)$. SE_{ij} is the standard error of the j^{th} odds ratio from the i^{th} study. σ^2 is the extra variation from the random effects model. The x_{ij} are the fixed terms that describe the time period covered by that particular odds ratio. The β_j ($j=1, \ldots, k$) are the odds ratios to be estimated for each duration interval.

We originally assumed that there was a term for each year (up to 10) and a final term for greater than 10 years. However, the large number of terms resulted in very unstable estimates. For that reason, we broke the time points into 4 intervals: (1) 1 to 12 months, (2) 13 to 60 months, (3) 61 to 120 months, and (4) more than 120 months. We then used the x_{ij} to create the time period desired. For example, if the first interval were from 1 to 36 months, then the vector of x_{ij} would be (1/3, 2/3, 0, 0, 0). This would reflect that one-third of the patients in the interval were in the 1 to 12 month interval and two-thirds of the patients were in the 13 to 60 month interval. Using this methodology, any interval could be described. The model was fitted using

SAS PROC NLMIXED (SAS Institute Inc.; Cary, NC; 2009) with "subject" set to the particular study, *i*.

Time Since Last OC Use

Using the equation above, we grouped time since last OC use into 4 intervals: (1) 0 to 5 years, (2) 5 to 10 years, (3) 10 to 20 years (4) more than 20 years. We then used the x_{ij} to create the time period desired. For example, if the first interval were from 1 to 15 years, then the vector of x_{ij} would be (2/3, 1/3, 0, 0, 0). This would reflect that two-thirds of the patients in the interval were in the 0 to 10 year interval and one-third of the patients were in the 10 to 20 year interval. Using this methodology, any interval could be described. The model was fitted using SAS PROC NLMIXED (SAS Institute Inc.; Cary, NC; 2009) with "subject" set to the particular study, *i*.

Results

This section presents results of our detailed analysis of the relationship between OCs and the following outcomes:

- Breast cancer incidence and mortality
- Cervical cancer incidence and mortality
- Colorectal cancer incidence and mortality
- Endometrial cancer incidence and mortality

OC Use and Breast Cancer Incidence

We identified 44 studies that evaluated the association between OC use and the incidence of breast cancer.[37,88,94,99,138,139,155,156,183-228] Of these, 29 were case-control studies, 14 cohort studies, and 1 pooled analysis; 19 studies were rated good quality, 25 fair quality, and 3 poor quality. Roughly half of the studies (21) assembled cohorts fully or partially based in the United States (Table 18).

Table 18. Study characteristics and association between OC use and breast cancer incidence

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Shapiro, 2000[185]	Black or Colored women aged 20–54 yr in Cape Town Cases: 484 invasive breast cancer, hospital Controls: 1625, hospital Recruitment period: 1994–1997	1.2	1.0 to 1.5	Age, sex, injectable progesterone use, ethnicity	South Africa	Fair	1
Van Hoften, 2000[186]	Women aged 41–52 yr in Doorlopend Onderzoek Morbiditeit/Mortaliteit Cohort Study Cases: 309 incident breast cancer, breast cancer screening program Controls: 610 cohort members Recruitment period: 1982–1984	1.24	0.96 to 1.78	Age, parity, menopausal status, age at menarche, smoking, marital status, education, age at first delivery, maternal history of breast cancer	Netherlands	Good	1
Gomes, 2001[187]	Hospital patients in Belo Horizonte (age NR) Cases: 280 breast cancer, hospital Controls: 569 outpatients or gynecology inpatients Recruitment period: 1978–1987	1.93	1.19 to 3.11	Parity, menopausal status, family history, occupation (housewife, housekeeper, other) irregular menstrual cycles, and possibly other (hard to tell)	Brazil	Poor	1

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Moorman, 2001[188]	Women aged 20–74 yr in Carolina Breast Cancer Study *White <50 yr* Cases: 328 invasive breast cancer, registry Controls: 236, DMV or Medicare lists *African American <50 yr* Cases: 175 invasive breast cancer, registry Controls: 171, DMV or Medicare lists *White ≥50 yr* Cases: 195 invasive breast cancer, registry Controls: 221, DMV or Medicare lists *African American ≥50 yr* Cases: 160 invasive breast cancer, registry Controls: 161, DMV or Medicare lists Recruitment period: 1993–1996	1.27 1.41 0.95 0.90	0.76 to 2.21 0.82 to 2.41 0.59 to 1.53 0.51 to 1.57	Age, family history, age at menarche, breastfeeding , age at first pregnancy, age at menopause	U.S.	Fair	1
Heimdal, 2002[189]	Women aged 40–60 yr from breast cancer families in a cancer family clinic Cases: 380 breast cancer Controls: 1043 Recruitment period: 1999	0.90	0.68 to 1.19	Parity, age at menarche, BRCA1 mutation status	Norway	Fair	2
Marchbanks, 2002[183]	Women aged 35–64 yr in Women's Contraceptive and Reproductive Experiences (CARE) Study Cases: 4575 breast cancer, SEER registries Controls: 4682, community Recruitment period: 1994–1998	0.9	0.80 to 1.01	Age, race, parity, menopausal status, BMI, family history, age at menarche, study site, age at menopause, age at first term pregnancy, hormone replacement therapy	U.S.	Good	1

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Narod, 2002[190]	Known carriers of BRCA1 or BRCA2 mutations *BRCA1 carriers* Cases: 981 breast cancer, research studies Controls: 981, research studies *BRCA2 carriers* Cases: 330 breast cancer, research studies Controls: 330, research studies Mean age of cases at diagnosis: 39.1 yr (SD 8.1) Recruitment period: 1977–2001	1.20 0.94	1.02 to 1.40 0.72 to 1.24	Race, parity	52 centers in 11 countries	Fair	3
Tryggvadottir, 2002[227]	All Icelandic women diagnosed with first invasive breast cancer from 1979–1995 Cases: 1120, registry Controls: 10,537, registry Recruitment period: 1979–1995	NR	NR	NA	Iceland	Good	5
Althuis, 2003[191]	Premenopausal women aged 20–54 yr Cases: 265 breast cancer, <35 yr Controls: 280 community controls, <35 yr Cases: 1214 breast cancer, 35–44 yr Controls: 1033 community controls, 35–44 yr Cases: 271 breast cancer, 45–54 yr Controls: 244 community controls, 45–54 yr Recruitment period: 1990–1992	0.73 1.13 2.03	0.5 to 1.1 0.9 to 1.4 1.3 to 3.1	Age, race, BMI, age at menarche, study site, number of mammograms within 5 yr prior to diagnosis, recent oral contraceptive use, a combination variable for age at birth and number of full-term births, family history of breast cancer, alcohol consumption	U.S.	Good	1
Althuis, 2003[192]	Women aged 20–54 yr in 5 metropolitan areas Cases: 1640 invasive or *in situ* breast cancer, registries Controls: 1492 no breast cancer, community Recruitment period: 1990–1992	NR	NR	NA	U.S.	Fair	4

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Newcomer, 2003[193]	Women <75 yr in Collaborative Breast Cancer Study Cases: 5510 breast cancer, registries Controls: 9311, community Note: ductal cancer only (lobular cancer cases excluded) Recruitment period: NR	1.00	0.90 to 1.11	Age, race, BMI, family history, type of and age at menopause, state, education, alcohol	U.S.	Fair	10
Norman, 2003[194]	Women aged 35–64 yr in Women's Contraceptive and Reproductive Experiences (CARE) Study Cases: 1847 breast cancer, SEER registries Controls: 1932, community Recruitment period: 1994–1998	NR	NR	NA	U.S.	Fair	5
Suter, 2003[195]	Women <45 yr in Western Washington Cases: 524 breast cancer, SEER registry Controls: 461, community Recruitment period: 1990–1992	1.3	0.9 to 1.8	Age	U.S.	Fair	1
Wrensch, 2003[228]	Residents of Marin County, California *All subjects* Cases: 285, registry Controls: 286, community *Age <50* Cases: 201, registry Controls: 201, community *Age >50* Cases: 84, registry Controls: 85, community Recruitment period: 1997–1999	0.43 0.41 0.15	0.26 to 0.72 0.22 to 0.75 0.03 to 0.65	Age, residence at birth	U.S.	Good	1

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Fowke, 2004[196]	Women aged 25–70 yr in Shanghai Breast Cancer Study *Premenopausal* Cases: 103 breast cancer, hospitals and registry Controls:103, resident registry *Postmenopausal* Cases: 110 breast cancer, hospitals and registry Controls: 127, resident registry Recruitment period: 1996–1998	0.92 0.96	0.67 to 1.26 0.70 to 1.32	Age, parity, BMI, age at menarche, education, fibroadenoma history, leisure time activity, age at first live birth	China	Fair	9
Jernstrom, 2005[197]	Women <40 yr in South Swedish Health Care Region Cases: 245 breast cancer, registry Controls: 735, community Recruitment period: 1990–1995	1.65	0.95 to 2.87	Parity, family history, age at menarche, smoking	Sweden	Fair	4
Milne, 2005[198]	Women <40 yr in San Francisco, Ontario, Melbourne, and Sydney *Cases with BRCA1 mutation* Cases: 47 breast cancer, registries Controls: 815, community *Cases with BRCA2 mutation* Cases: 36 breast cancer, regional registries Controls: 815, community *Cases with neither BRCA1 or 2 mutations* Cases: 1073 breast cancer, registries Controls: 815, community Recruitment period: 1995–1998	0.22 1.02 0.93	0.10 to 0.49 0.34 to 3.09 0.69 to 1.24	Age, parity, family history, age at menarche, study location/period, education, marital status, country of birth	U.S., Canada, Australia	Good	4

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Gronwald, 2006[94]	BRCA1 carriers, Hereditary Cancer Center (age NR) Cases: 348 breast cancer, cancer center Controls: 348, cancer center Recruitment period: NR	0.80	0.50 to 1.20	NR	Poland	Fair	3
Haile, 2006[199]	White women <40 yr BRCA1 or BRCA2 carriers *BRCA1 carriers (cases and controls)* Cases: 111 breast cancer, registries Controls: 185, registries *BRCA2 carriers (cases and controls)* Cases: 71 breast cancer, registries Controls, 94, registries Recruitment period: NR	0.64 1.29	0.35 to 1.16 0.61 to 2.76	Age, parity, family history, study site	U.S., Canada, Australia	Good	3
Ma, 2006[201]	Women aged 35–64 yr in Women's Contraceptive and Reproductive Experiences (CARE) Study Cases: 1725 breast cancer, SEER registries Controls: 440, community Recruitment period: 1994–1998	NR	NR	NA	U.S.	Good	5
Rosenberg, 2006[200]	Extension of a case-control study among Swedish residents aged 50–74 yr Cases: 2289 ductal, lobular, or tubular cancer, registries Controls: 3065, population registry Recruitment period: 1993–1995	NR	NR	NA	Sweden	Fair	5
Faheem, 2007[202]	Hospital patients in Islamabad Cases: 150,breast cancer, hospital Controls: 159, community Mean age of cases: 42 yr (SD 12) Recruitment period: 2005	NR	NR	NA	Pakistan	Poor	5

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Folger, 2007[203]	Women aged 35–64 yr with history of short-term OC use, Women's CARE study *Premenopausal* Cases: 497 breast cancer, SEER registries Controls: 456, community *Postmenopausal* Cases: 729 breast cancer, SEER registries Controls: 707, community Recruitment period: 1994–1998	NR	NR	NR	U.S.	Fair	5
Nichols, 2007[204]	Women aged 20–74 yr in Collaborative Breast Cancer Study Cases: 1878 breast cancer *in situ,* registry Controls: 8041, community Recruitment period: 1997–2001	1.10	0.99 to 1.25	Age, parity, menopausal status, family history, age at menarche, smoking, state, age at first birth, age at menopause, HRT, weight at age 18, height, weight gain since age 18, education, mammography screening, history of benign breast disease	U.S.	Good	6

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Shantakumar, 2007[205]	Long Island Breast Cancer Study Project (age NR) *Premenopausal women* Cases: 468 *in situ* or invasive breast cancer, rapid case ascertainment Controls: 500, community *Postmenopausal <65 years old* Cases: 491 *in situ* or invasive breast cancer, registry, rapid case ascertainment Controls: 554, community *Postmenopausal >65 years old* Cases: 519 *in situ* or invasive breast cancer, registry Controls: 439, community Recruitment period: 1996–1997	0.82 0.95 1.37	0.57 to 1.19 0.74 to 1.22 1.04 to 1.81	Age	U.S.	Good	1
Sweeney, 2007[206]	Hispanic and non-Hispanic white women ≤64 yr *All subjects* Cases: 2303 breast cancer, registries Controls: 2513, community *Hispanics only* Cases: 796 breast cancer, registries Controls: 919, community *Non-Hispanic Whites* Cases: 1522 breast cancer, registries Controls: 1586, community Recruitment period: 1999–2004	1.08 1.08 1.10	0.94 to 1.24 0.90 to 1.29 0.88 to 1.37	Age, parity, menopausal status, family history, study center, education, alcohol, language acculturation, years since last birth, use of contraception injections and HRT	U.S.	Good	1

00803372

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Figueiredo, 2008[207]	Women <55 yr in Women's Environment, and Radiation Epidemiology Study *Women with history of unilateral breast cancer* Cases: 708 asynchronous bilateral breast cancer, registry Controls: 1399 unilateral breast cancer only, registry Recruitment period: 1985–2000	0.88	0.67 to 1.16	Parity, menopausal status, family history, age at menarche, counter-matching sampling, age at diagnosis of first breast cancer, family history of breast cancer in a first degree relative, histology, stage, chemotherapy, hormonal therapy, radiation therapy	U.S.	Fair	7
Lee, 2008[208]	Women aged 20–49 yr in Women's Learning the Influence of Family and Environment Study Cases: 94, breast cancer and BRCA1/2 carrier, registry Controls: 444 BRCA1/2 unknown, community Cases: 1375 breast cancer, not BRCA1/2 carrier, registry Controls: 444 BRCA1/2 unknown, community Recruitment period: 1998–2003	0.68 0.81	0.33 to 1.38 0.57 to 1.14	Age, race, parity, family history, education, Ashkenazi Jewish	U.S.	Good	3 1
Nyante, 2008[209]	Women aged 20–44 yr in Women's Interview Study of Health *Ductal cancer* Cases: 1164 invasive or *in situ* cancer, rapid reporting system Controls: 1501, community *Lobular cancer* Cases: 100, invasive or *in situ* cancer, rapid reporting system Controls: 1501, community Recruitment period: 1990–1992	1.21 1.10	1.01 to 1.45 0.68 to 1.78	Age, site, frequency of pap smears	U.S.	Fair	4

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Phillips, 2009[211]	Women aged 20–74 yr in Carolina Breast Cancer Study Cases: 1808 invasive breast cancer, registry Controls: 1564, community Cases: 446 *in situ* cancer, registry Controls: 458, community Recruitment period: 1993–2001	1.11 1.11	0.94 to 1.32 0.80 to 1.53	Age, race	U.S.	Fair	1
Rosenberg, 2009[210]	Women aged 25–69 yr in Case-Control Surveillance Study *Cases: all invasive cancers* Cases: 907 breast cancer, hospital Controls: 1711, hospital *Age <50* Cases: 431 breast cancer, hospital Controls: 939, hospital *Age ≥50* Cases: 476 breast cancer, hospital Controls: 772, no breast cancer, hospital *Black women* Cases: 176 breast cancer, hospital Controls: 559, hospital *White women* Cases: 731 breast cancer, hospital Controls: 1152, hospital Recruitment period: 1976–1996	NR	NR	NA	U.S.	Fair	5

00803374

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Figueiredo, 2010[212]	Women <55 yr in Women's Environment, and Radiation Epidemiology Study *BRCA1 carriers (cases and controls)* Cases: 67 contralateral breast cancer, registry Controls: 42 unilateral breast cancer, registry *BRCA2 carriers (cases and controls)* Cases: 41 contralateral breast cancer, registry Controls: 31 contralateral breast cancer, registry Recruitment period: 1985–2000	0.82 2.38	0.21 to 3.13 0.72 to 7.83	Age	U.S.	Fair	7
Lumachi, 2010[213]	Women who underwent curative surgery for breast cancer *Postmenopausal women* Cases: 238 breast cancer, surgically treated Controls: 255, mammography screening Mean age of cases at diagnosis: 62 yr (SD 10) Recruitment period: NR	2.06	1.14 to 3.70	Unadjusted	Italy	Fair	1

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Ma, 2010[214]	White or African-American women aged 35–64 yr Cases: 335 triple-negative breast cancer, registries Controls: 2015, community Cases: 97 ER-/PR/HER2+ breast cancer, registries Controls: 2015, community Cases: 645 luminal A breast cancer, registries Controls: 2015, community Cases: 120 luminal B breast cancer, registries Controls: 2015, community Recruitment period: 2000–2003	0.93 1.00 1.21 1.23	0.74 to 1.17 0.72 to 1.39 0.69 to 2.11 0.73 to 2.10	Age, race, parity, menopausal status, BMI, family history, age at menarche, study site, education	U.S.	Good	8
Xu, 2011[224]	Women aged 25–65 yr in Shanghai Breast Cancer Study Cases: 2073 breast cancer, hospitals and registry Controls: 2084, resident registry Recruitment periods: 1996–1998; 2002–2005	0.98	0.83 to 1.15	Age, parity, menopausal status, BMI, family history, age at menarche, education	China	Good	1
Marchbanks, 2012[226]	White or black women aged 35–64 yr Cases: 2282, registries Controls: 2424, community Recruitment period: 1994–1998	NR	NR	NA	U.S.	Good	5

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Case-Control (continued)							
Urban, 2012[155]	Black South African women aged 18–79 yr Cases: 256, hospital Controls: 156, hospital Recruitment period: 1995–2006	1.28	1.0 to 1.64	Age, parity, smoking, year of diagnosis, education, alcohol consumption, sexual partners, urban/rural residence, province of birth	South Africa	Good	1
Cohort							
Grabrick, 2000[215]	Family members of women aged 21–88 yr diagnosed with breast cancer between 1944 and 1952 Exposed: 3156 Unexposed: 2994 Recruitment period: 1991–1996	1.4	1.0 to 2.0	Age, birth cohort, class effect of family	U.S.	Good	2
Kumle, 2002[216]	Women aged 30–49 yr in prospective cohort study Exposed: 74,856 Unexposed: 28,171 Recruitment period: 1991–1992	1.3	1.1 to 1.5	Age, parity, menopausal status, BMI, family history, age at menarche, breastfeeding , age at first birth, HRT use, region, BMI times menopausal status	Norway, Sweden	Good	1
Dumeaux, 2003[217]	Women aged 30–70 yr in Norwegian Women and Cancer Study Exposed: 49,322 Unexposed: 37,690 Recruitment period: 1991–1997	1.25	1.07 to1.46	Age, parity, menopausal status, BMI, family history, age at menarche, geographic area, invitation of breast cancer screening, age at first birth, HRT use, alcohol consumption	Norway	Fair	1

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Dumeaux, 2005[218]	E3N-EPIC Cohort women aged 40–60 yr Exposed: 28,251 Unexposed: 40,419 Recruitment period: 1990	0.91	0.81 to 1.03	Parity, BMI, family history, age at menarche, frequency of pap smears, history of benign breast disease, alcohol consumption, time since menopause	France	Fair	1
Silvera, 2005[219]	Women aged 40–59 yr in Canadian National Breast Screening Study *Women with first- or second-degree relatives with breast cancer* Exposed: 962 Unexposed: 745 *Women with first-degree relatives with breast cancer* Exposed: 433 Unexposed: 362 *Women with second-degree relatives with breast cancer* Exposed: 414 Unexposed: 284 Recruitment period: 1980–1985	0.88 1.03 0.74	0.73 to 1.07 0.78 to 1.38 0.54 to 1.00	Age, parity, menopausal status, BMI, age at menarche, alcohol, history of breast disease, age at first birth, HRT use, study center, randomization group	Canada	Good	2
Vessey, 2006[156]	Women aged 25–39 yr at study entry in Oxford Family Planning Association Contraceptive Study Exposed: 301,000 person-years Unexposed: 187,000 person-years Recruitment period: 1968–1974	1.0	0.8 to 1.1	Age, parity, BMI, breastfeeding, social class, height, age at first term pregnancy, age at first marriage	UK	Good	1
Brohet, 2007[220]	Women aged 19–74 yr in International BRCA1/2 Carrier Cohort Study Exposed: 21,569 person-years Unexposed: 43,611 person-years Recruitment period: NR	1.47	1.16 to 1.87	Age, parity, family clustering, history of oophorectomy before right censoring	UK, France, Netherlands	Fair	3

Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Hannaford, 2007[37]	Royal College of General Practitioner's Oral Contraception Study Exposed: 744,000 person-years Unexposed: 339,000 person-years Mean age at entry: 29 yr (SD 6.6) Recruitment period: 1968–NR	0.98	0.87 to 1.10	Age, parity, smoking, social status; ever use HRT	UK	Fair	1
Lund, 2007[221]	Women aged 34–70 yr in Norwegian Women and Cancer Study Exposed: 11,371 Unexposed: 18,747 Recruitment period: 1991–1997	1.33	1.11 to 1.59	Parity, BMI, family history, age at menarche, mammography, age at first delivery	Norway	Good	1
Dorjgochoo, 2009[88]	Women aged 40–70 yr in Shanghai Women's Health Study Exposed: 12,957 Unexposed: 15,557 Recruitment period: 1997–2000	1.05	0.84 to 1.31	Age, parity, menopausal status, BMI, family history, age at menarche, smoking, breastfeeding , education, physical activity, other contraceptive methods	China	Fair	1
Rosenblatt, 2009[138]	Textile Workers aged 30–64 yr in Shanghai Exposed: 352,695 person-years Unexposed: 2,057,377 person-years Recruitment period: 1989–1991	0.9	0.78 to 1.03	Age, parity	China	Poor	1
Hunter, 2010[222]	Nurses' Health Study II of women aged 24–43 yr at study entry Exposed: 1,070,386 person-years Unexposed: 176,581 person-years Recruitment period: 1989–2001	NR	NR	NA	U.S.	Good	4

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Cohort (continued)							
Rosenberg, 2010[223]	Women aged 21–69 yr in Black Women's Health Study Exposed: 445,824 person-years Unexposed: 128,768 person-years *ER+/PR+ receptor status* Cases: 284 *ER+/PR- receptor status* Cases: 80 *ER-/PR- receptor status* Cases: 46 Recruitment period: 1995	IRR=1.11 IRR=0.97 IRR=1.65	0.86 to 1.42 0.61 to1.54 1.19 to 2.30	Age, parity, BMI, family history, age at menarche, education, age at first birth, age at menopause, HRT, exercise, alcohol, questionnaire cycle	U.S.	Fair	8
Bernholtz, 2011[225]	Jewish women at high risk of developing breast or ovarian cancer *BRCA1 or BRCA2 carriers* Exposed: 403 Unexposed: 373 *BRCA1 carriers* Exposed: 309 Unexposed: 182 *BRCA2 carriers* Exposed: 136 Unexposed: 72 Recruitment period: 1996–2010	1.84 1.72 2.07	1.47 to 2.31 1.31 to 2.25 1.34 to 3.20	Age at menarche, breastfeeding, year of birth	Israel	Fair	3

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Table 18. Study characteristics and association between OC use and breast cancer incidence (continued)

Study[a]	Study Details	OR[b]	95% CI	Covariates	Region	Study Quality	Meta-Analysis Code[c]
Pooled							
Dolle, 2009[184]	Women aged 21–45 yr in Seattle-Puget Sound Cases: 897 with invasive cancer; 187 with triple negative cancer; registries Controls: 1569, not reported Recruitment periods: 1983–1990; 1990–1992	1.3 (all subjects) 2.5 (triple-negative subjects)	1.0 to 1.7 1.4 to 4.3	Age, family history, breastfeeding history, oral contraceptive duration	U.S.	Fair	8

BMI = body mass index; CI = confidence interval; DMV = department of motor vehicles; ER = estrogen receptor; HRT = hormone replacement therapy; IRR = incidence rate ratio; NR = not reported; NZ = New Zealand; OC = oral contraceptive; OR = odds ratio; PR = progesterone receptor; SEER = Surveillance, Epidemiology, and End Results registry; UK = United Kingdom; U.S. = United States; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

[b]Odds ratios for meta-analysis of ever versus never OC use.

[c]Meta-analysis code: 1= Included in meta-analysis; 2 = Excluded due to family history of breast cancer; 3 = Excluded due to BRCA mutation carriers; 4 = Excluded due to age at diagnosis ≤45 yr; 5 = Excluded due to overall ever versus never OR not reported or not calculable; 6 = Excluded due to cancer in situ only; 7 = Excluded due to all cases and controls having breast cancer; 8 = Excluded due to ER/PR/HER2 subtypes; 9 = Excluded due to data are subset of Shanghai Breast Cancer Study[224]; 10 = Excluded due to targeting certain subtypes of cancer only.

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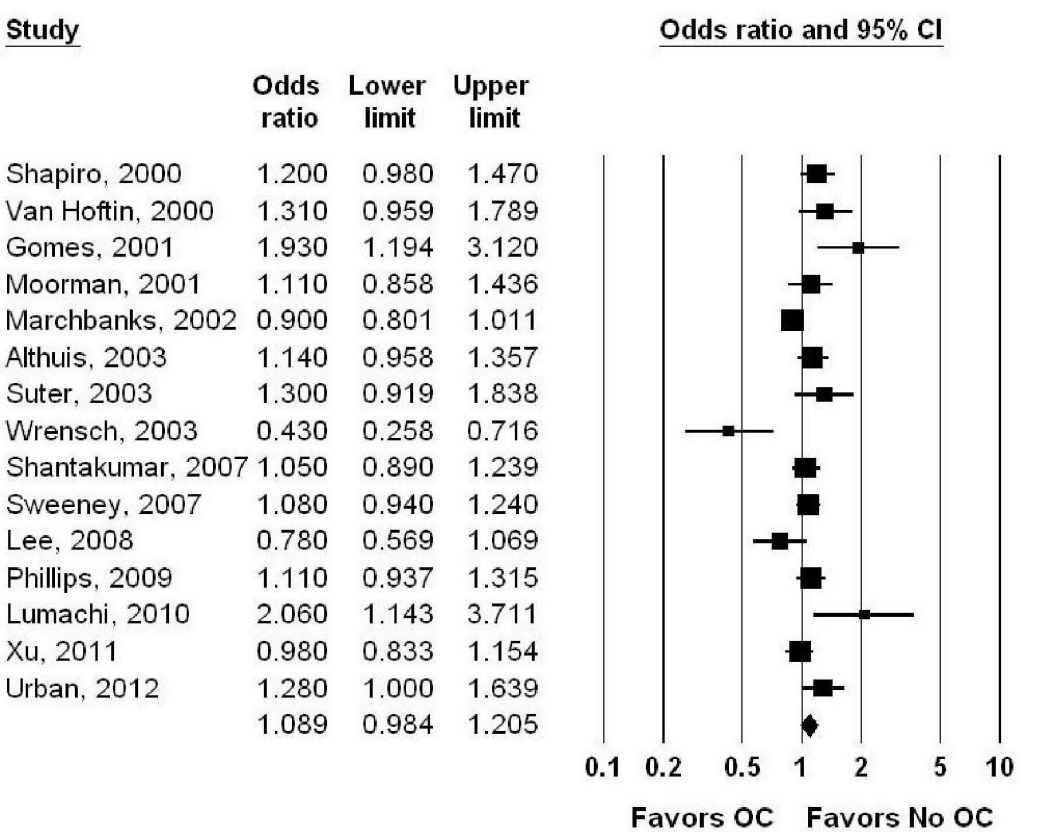
Ever Versus Never OC Use

Fifteen case-control studies representing 38,682 women[155,183,185-188,191,195,205,206,208,211,213,224,228] were included in this meta-analysis examining the effect of ever versus never OC use on the incidence of breast cancer (Table 18). Of these studies, nine were rated good quality, five fair quality, and one poor quality. Abstracted data not included in this analysis are specified (with rationale) in Table 18. Reasons for exclusion from this analysis included the following: study populations representing specialized subgroups (e.g., BRCA mutation populations, family history, cancer subtype); reporting a subset of results from the same study as another article already included in the analysis; and not reporting an odds ratio for ever versus never OC use. Some studies gave results only by subgroup; however, in some instances we were able to combine the subgroups to calculate the odds ratio for the entire study population. Figure 23 shows the results; ever use of OCs increased the risk of breast cancer compared with never use, but the confidence interval included 1 (OR 1.09; 95% CI, 0.98 to 1.21).

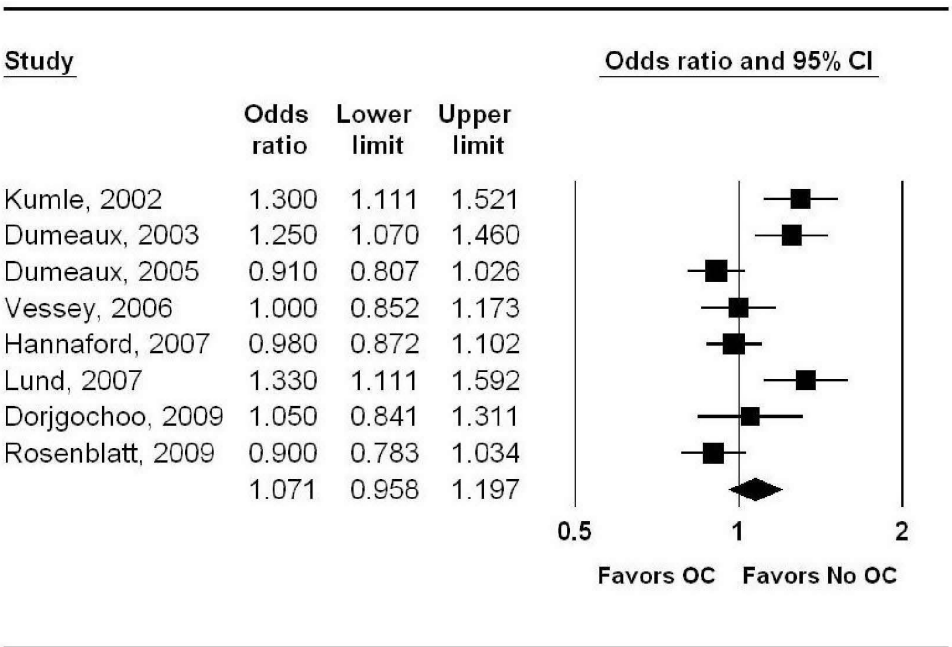
Figure 23. Forest plot for ever versus never OC use (case-control studies, breast cancer incidence)



CI = confidence interval; OC = oral contraceptive

Eight cohort studies representing 317,341 women across five studies and 3,981,072 person-years across three studies[37,88,138,156,216-218,221] met inclusion criteria for this meta-analysis (Table 18). Of these studies, three were rated good quality, four fair quality, and one poor quality. Abstracted data not included in this analysis are specified (with rationale) in Table 18. Reasons for exclusion from this analysis included the following: study populations representing specialized subgroups; and not computing an effect size for ever use versus never OC use. As shown in Figure 24, the odds ratio for ever versus never use of OCs was similar to that for the case-control studies (OR 1.07; 95% CI, 0.96 to 1.20).

Figure 24. Forest plot for ever versus never OC use (cohort studies, breast cancer incidence)



CI = confidence interval; OC = oral contraceptive

The pooled effect sizes for the two groups were similar, with a test for a difference resulting in a p-value of 0.81. Therefore, we combined case-control studies and cohort studies. Across all included studies, results suggest that a history of OC use slightly but significantly increases the incidence of breast cancer compared with women who never used OCs. The odds ratio was 1.08 (95% CI, 1.00 to 1.17), with a Q-value of 73.35 for 21 degrees of freedom, $p<0.001$.

Sensitivity Analyses

Analyses were repeated excluding the one cohort study rated poor quality. This exclusion had a minor effect on the odds ratio estimates for all studies combined (OR 1.08; 95% CI, 1.00 to 1.16). We also conducted sensitivity analyses among U.S.-based studies only; effect sizes were smaller and no longer statistically significant (OR 1.03; CI, 0.93 to 1.14).

Duration of OC Use

Fourteen studies[138,156,183,185,188,194,195,201,205,206,211,216-218,228] were included in this meta-analysis examining the effect of duration of OC use on breast cancer incidence (Table 19). Of these, 9 were case-control studies. Six studies were rated good quality, eight fair quality, and one poor quality. We did not include data in the meta-analysis for studies that were conducted in a special population, did not have at least 3 categories for duration of use, or used a referent category other than never users.

Table 19. Data for outcomes on duration of use (breast cancer incidence)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
		Case-Control		
Shapiro, 2000[185]		< 1 yr 1–4 yr 5–9 yr > 10 yr	1.3 1.3 1.4 1.2	0.8 to 1.4 1.0 to 1.8 0.9 to 2.1 0.7 to 2.3
Van Hoften, 2000[186]	Total sample	1–10 yr > 10 yr	1.27 1.43	0.92 to 1.77 0.92 to 2.22
	Women ≤55 yr	1–10 yr > 10 yr	1.25 1.22	0.85 to 1.82 0.72 to 2.07
	Women ≥56 yr	1–10 yr > 10 yr	1.26 2.05	0.74 to 2.14 1.07 to 3.95
Moorman, 2001[188]	White women <50 yr	≤ 1 yr 1–5 yr 5–10 yr > 10 yr	1.29 1.49 0.94 1.41	0.68 to 2.47 0.85 to 2.64 0.52 to 1.70 0.74 to 2.70
	African-American women <50 yr	≤ 1 yr 1–5 yr 5–10 yr > 10 yr	1.29 1.23 1.64 1.61	0.61 to 2.72 0.66 to 2.32 0.82 to 3.28 0.77 to 3.35
	White women ≥50 yr	≤ 1 yr 1–5 yr 5–10 yr > 10 yr	0.92 0.90 0.80 1.34	0.49 to 1.73 0.43 to 1.89 0.38 to 1.67 0.59 to 3.07
	African-American women ≥50 yr	≤ 1 yr 1–5 yr 5–10 yr > 10 yr	0.90 0.39 2.06 1.37	0.40 to 2.01 0.16 to 0.99 0.77 to 5.53 0.27 to 6.90
Marchbanks, 2002[183]		< 1 yr 1 to < 5 yr 5 to < 10 yr 10 to < 15 yr	0.9 0.9 0.9 0.8	0.8 to 1.1 0.8 to 1.0 0.8 to 1.0 0.7 to 1.0
Narod, 2002[190]	BRCA1 carriers	0–4 yr 5–9 yr 10–14 yr 15–30 yr	1.10 1.36 1.27 1.30	0.92 to 1.31 1.11 to 1.67 0.99 to 1.64 0.91 to 1.87
	BRCA2 carriers	0–4 yr 5–9 yr 10–14 yr 15–30 yr	0.90 0.82 1.16 1.35	0.67 to 1.20 0.56 to 1.91 0.75 to 1.78 0.71 to 2.56

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control (continued)				
Newcomer, 2003[193]	Ductal carcinoma vs. controls	< 1 yr 1–4 yr 5–9 yr 10–14 yr > 15 yr	1.1 1.0 1.0 1.0 1.0	1.0 to 1.3 0.9 to 1.1 0.9 to 1.2 0.9 to 1.3 0.7 to 1.3
	Lobular carcinoma vs. controls	< 1 yr 1–4 yr 5–9 yr 10–14 yr > 15 yr	1.4 1.1 1.1 1.1 1.7	1.0 to 2.0 0.8 to 1.6 0.7 to 1.7 0.7 to 1.9 0.9 to 3.5
Norman, 2003[194]		< 0.5 yr 0.5 to < 2 yr 2 to < 5 yr 5 to < 10 yr > 10 yr	0.73 0.91 0.83 0.81 0.62	0.5 to 1.05 0.63 to 1.31 0.56 to 1.22 0.55 to 1.19 0.41 to 0.95
Suter, 2003[195]		< 1 yr 5 to <10 yr > 10 yr	1.3 1.4 1.2	0.9 to 1.8 0.9 to 2.1 0.7 to 1.8
Wrensch, 2003[228]		< 2 yr 2-6 yr 6-10 yr >10 yr	0.55 0.52 0.57 0.47	0,33 to 0.93 0.30 to 0.89 0.32 to 1.00 0.27 to 0.82
Dumeaux, 2005[218]		< 5 yr 5–9 yr > 10 yr	0.94 0.91 0.87	0.81 to 1.09 0.75 to 1.11 0.72 to 1.06
Milne, 2005[198]	BRCA1 carriers	1–4 yr 5–9 yr > 10 yr	0.25 0.22 0.20	0.09 to 0.70 0.09 to 0.58 0.08 to 0.54
	BRCA2 carriers	1–4 yr 5–9 yr > 10 yr	0.97 1.34 0.73	0.26 to 3.56 0.41 to 4.45 0.20 to 2.65
	Noncarriers	1–4 yr 5–9 yr > 10 yr	0.76 0.97 1.02	0.54 to 1.07 0.70 to 1.34 0.74 to 1.41
Gronwald, 2006[94]		< 2 yr ≥ 2 yr	0.9 0.8	0.5 to 1.2 0.5 to 1.4
Haile, 2006[199]	BRCA1 carriers	1–4 yr ≥ 5	0.61 0.61	0.31 to 1.17 0.32 to 1.16
	BRCA2 carriers	1–4 yr ≥ 5 yr	0.79 1.45	0.26 to 2.37 0.64 to 3.27
Ma, 2006[201]		< 1 yr 1–4 yr 5–9 yr > 10 yr	0.78 0.80 0.62 0.84	0.51 to 1.18 0.54 to 1.19 0.42 to 0.93 0.56 to 1.26

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control (continued)				
Rosenberg, 2006[200]	Ductal breast cancer	< 5 yr > 5 yr	0.9 0.9	0.7 to 1.0 0.7 to 1.1
	Lobular cancer	< 5 yr > 5 yr	0.6 0.9	0.4 to 0.9 0.6 to 1.4
	Tubular cancer	< 5 yr > 5 yr	1.3 1.0	0.7 to 2.2 0.5 to 1.9
Folger, 2007[203]	Premenopausal	< 6 mo	1.3	0.60 to 1.0
	Postmenopausal	< 6 mo	0.8	0.60 to 1.28
Nichols, 2007[204]		1–1.9 yr 2–2.4 yr 4.5–8.9 yr > 9 yr	1.13 1.22 1.04 1.06	0.96 to 1.33 1.04 to 1.44 0.86 to 1.25 0.88 to 1.27
Shantakumar, 2007[205]	Premenopausal women	< 6 mo 6–12 mo 13–60 mo > 60 mo	1.31 1.38 1.27 1.54	0.68 to 2.55 0.93 to 2.03 0.90 to 1.79 1.06 to 2.24
	Postmenopausal <65 yr	< 6 mo 6–12 mo 13–60 mo > 60 mo	1.52 0.78 0.88 1.01	0.77 to 3.03 0.53 to 1.16 0.60 to 1.28 0.69 to 1.48
	Postmenopausal >65 yr	< 6 mo 6–12 mo 13–60 mo > 60 mo	0.93 0.51 1.15 0.86	0.23 to 3.77 0.27 to 0.95 0.58 to 2.31 0.44 to 1.66
Sweeney, 2007[206]	Hispanics only	< 5 yr 5–9 yr 10–19 yr > 20 yr	1.14 1.06 1.03 1.43	0.87 to 1.49 0.77 to 1.46 0.74 to 1.43 0.69 to 2.95
	Non-Hispanic whites	< 5 yr 5–9 yr 10–19 yr > 20 yr	1.14 0.99 0.96 1.49	0.93 to 1.40 0.78 to 1.25 0.75 to 1.23 0.96 to 2.30
Figueiredo, 2008[207]		< 5 yr ≥ 5 yr	0.88 0.82	0.65 to 1.20 0.61 to 1.10
Lee, 2008[208]	BRCA1/2 carriers	< 4 yr 5–9 yr ≥ 10 yr	0.65 0.78 0.63	0.30 to 1.42 0.34 to 1.77 0.26 to 1.51
	Noncarriers	≤ 4 yr 5–9 yr ≥ 10 yr	0.80 0.66 0.95	0.55 to 1.16 0.45 to 0.98 0.64 to 1.42
Nyante, 2008[209]	Ductal carcinoma	< 1 yr 1–3 yr > 4 yr	1.13 1.11 1.30	0.80 to 1.61 0.89 to 1.38 1.06 to 1.59
	Lobular breast carcinoma	< 1 yr 1–3 yr > 4 yr	1.63 1.23 0.92	0.72 to 3.65 0.70 to 2.14 0.53 to 1.59

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control (continued)				
Phillips, 2009[211]	Invasive breast carcinoma	< 5 yr 5–10 yr > 10 yr	1.06 1.15 1.21	0.88 to 1.28 0.93 to 1.42 0.94 to 1.56
	DCIS	< 5 yr 5–10 yr > 10 yr	0.75 1.27 0.94	0.49 to 1.15 0.79 to 2.04 0.59 to 1.49
Rosenberg, 2009[210]	All invasive breast cancers	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 1.6 1.9 1.7	1.0 to 1.6 1.2 to 2.1 1.4 to 2.7 1.0 to 2.9
	Women <50 yr	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 1.9 1.8 1.3	1.0 to 1.8 1.3 to 2.7 1.1 to 2.8 0.6 to 2.7
	Women >50 yr	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 1.3 2.0 2.4	0.9 to 1.8 0.8 to 2.0 1.2 to 3.5 1.0 to 5.5
	Black women	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 2.3 2.5 NR	0.8 to 2.1 1.3 to 3.9 1.3 to 4.7 NR
	White women	1–4 yr 5–9 yr 10–14 yr > 15 yr	1.3 1.4 1.8 1.4	1.0 to 1.7 1.0 to 1.9 1.2 to 2.5 0.8 to 2.6
Figueiredo, 2010[212]	BRCA1 carriers	< 5 yr ≥ 5 yr	2.91 2.07	0.75 to 11.30 0.60 to 7.11
	BRCA2 carriers	< 5 yr ≥ 5 yr	0.86 2.02	0.21 to 3.57 0.52 to 7.81
Ma, 2010[214]	Triple-negative breast cancer	< 1 yr 1–4 yr 5–9 yr ≥ 10 yr	0.94 0.93 1.12 1.06	0.63 to 1.42 0.63 to 1.36 0.75 to 1.66 0.70 to 1.61
	ER-/PR-/HER2+ breast cancer	< 1 yr 1–4 yr 5–9 yr ≥ 10 yr	1.22 1.15 0.86 1.59	0.61 to 2.43 0.59 to 2.23 0.40 to 1.85 0.81 to 3.10
	Luminal A breast cancer	< 1 yr 1–4 yr 5–9 yr ≥ 10 yr	0.98 1.04 0.78 0.87	0.73 to 1.32 0.79 to 1.37 0.57 to 1.06 0.63 to 1.19
	Luminal B breast cancer	< 1 yr 1–4 yr 5–9 yr ≥ 10 yr	1.17 1.12 1.50 1.20	0.62 to 2.24 0.60 to 2.07 1.80 to 2.78 0.62 to 2.32

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Case-Control (continued)				
Xu, 2011[224]		< 18 months ≥ 18 months	0.96 1.11	0.78 to 1.18 0.89 to 1.37
Marchbanks, 2012[226]	100 mcg mestranol/ 1.0 mg ethynodiol diacetate	< 2 yr ≥ 2 yr	0.8 0.8	0.4 to 1.5 0.5 to 1.1
	35 mcg ethinyl estradiol/0.5 mg norethindrone	< 2 yr ≥ 2 yr	1.2 1.2	0.7 to 2.0 0.6 to 1.4
	35 mcg ethinyl estradiol/1.0 mg norethindrone	< 2 yr ≥ 2 yr	0.9 1.0	0.6 to 1.4 0.8 to 1.4
	50 mcg mestranol/ 1.0 mg norethindrone	< 2 yr ≥ 2 yr	0.8 0.8	0.5 to 1.2 0.6 to 1.1
	80 mcg mestranol/ 1.0 mg norethindrone	< 2 yr ≥ 2 yr	0.6 0.8	0.4 to 0.99 0.6 to 1.0
	100 mcg mestranol/ 2.0 mg norethindrone	< 2 yr ≥ 2 yr	1.1 0.7	0.7 to 1.6 0.5 to 0.9
	100 mcg mestranol/ 2.5 mg norethindrone	< 2 yr ≥ 2 yr	0.8 1.0	0.4 to 1.4 0.6 to 1.7
	30 mcg ethinyl estradiol/0.3 mg norgestrel	< 2 yr ≥ 2 yr	1.5 0.8	0.9 to 2.6 0.5 to 1.1
	50 mcg ethinyl estradiol/0.5 mg norgestrel	< 2 yr ≥ 2 yr	1.1 0.6	0.6 to 2.0 0.4 to 0.98
	35 mcg ethinyl estradiol/0.5 mg (7 days), 0.75 mg (7 days), 1.0 mg (7 days) norethindrone	< 2 yr ≥ 2 yr	0.5 0.4	0.2 to 1.4 0.2 to 0.8

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
		Cohort		
Grabrick, 2000[215]		1–4 yr > 4 yr	1.5 1.3	1.0 to 2.3 0.9 to 1.9
Kumle, 2002[216]		< 5 yr 5–9 yr 10–14 yr > 15 yr	1.2 1.2 1.4 1.3	1.0 to 1.5 1.0 to 1.5 1.1 to 1.8 1.0 to 1.8
Dumeaux, 2003[217]		0–4 yr 5–9 yr > 10 yr	0.94 0.91 0.87	0.81 to 1.09 0.75 to 1.11 0.72 to 1.06
Silvera, 2005[219]	Women with any family history of breast cancer	1–12 mo 12–36 mo 36–84 mo > 84 mo	1.05 0.94 0.85 0.74	0.79 to 1.42 0.70 to 1.26 0.64 to 1.12 0.55 to 0.99
	Women with first-degree relatives of breast cancer	1–12 mo 12–36 mo 36–84 mo > 84 mo	1.18 1.24 1.07 0.75	0.75 to 1.38 0.82 to 1.88 0.72 to 1.59 0.47 to 1.19
	Women with second-degree relatives with breast cancer	1–12 mo 12–36 mo 36–84 mo > 84 mo	0.92 0.72 0.52 0.84	0.58 to 1.44 0.45 to 1.17 0.32 to 0.84 0.55 to 1.27
Vessey, 2006[156]		< 48 mo 49–96 mo > 97 mo	0.9 0.9 1.0	0.8 to 1.1 0.8 to 1.1 0.8 to 1.1
Brohet, 2007[220]		1–3 yr 4–8 yr > 9 yr	1.34 1.59 1.61	1.00 to 2.78 1.19 to 2.13 1.18 to 2.20
Hannaford, 2007[37]		< 48 mo 49–96 mo > 96 mo	1.00 0.95 1.22	0.81 to 1.23 0.75 to 1.21 0.97 to 1.52
Dorjgochoo, 2009[88]		< 2 yr > 2 yr	1.18 0.93	0.89 to 1.56 0.68 to 1.25
Rosenblatt, 2009[138]		1–11 mo 12–59 mo 60–119 mo > 120 mo	0.71 1.04 0.97 0.94	0.56 to 0.90 0.86 to 1.27 0.69 to 1.36 0.66 to 1.32
Hannaford, 2010[33]		< 4 yr 4–8 yr > 8 yr	0.92 0.87 1.13	0.64 to 1.34 0.58 to 1.31 0.75 to 1.70
Hunter, 2010[222]		0–8 yr > 8 yr	1.16 1.42	0.80 to 1.69 1.05 to 1.94

Table 19. Data for outcomes on duration of use (breast cancer incidence) (continued)

Study[a]	Subgroup (if Applicable)	Duration	OR	95% CI
Cohort (continued)				
Rosenberg, 2010[223]	ER+/PR+ breast cancers	< 5 yr 5–9 yr 10–14 yr > 15 yr	1.03 1.09 1.45 1.24	0.79 to 1.35 0.78 to 1.52 1.02 to 2.07 0.74 to 2.09
	ER-/PR- breast cancers	< 5 yr 5–9 yr 10–14 yr > 15 yr	1.67 1.37 1.83 2.25	1.18 to 2.36 0.89 to 2.11 1.11 to 2.90 1.23 to 4.11
	ER+/PR- breast cancer	< 5 yr 5–9 yr 10–14 yr > 15 yr	0.91 1.31 0.82 0.75	0.55 to 1.49 0.74 to 2.33 0.37 to 1.78 0.22 to 2.54
Pooled				
Dolle, 2009[184]	All subjects	1–2 yr 3–5 yr > 6 yr	1.3 1.4 1.3	0.9 to1.7 1.0 to 2.0 1.0 to1.8
	Women with triple-negative breast cancer	1–2 yr 3–5 yr > 6 yr	1.6 2.8 2.9	0.9 to 3.3 1.5 to 5.3 1.6 to 5.3

BRCA = breast cancer genetic mutation; CI = confidence interval; ER = estrogen receptor; mo = month/months; NR = not reported; OR = odds ratio; PR = progesterone receptor; yr = year/years

[a]Study identifies the primary abstracted article. For details about the relationships between companion studies and articles, refer to Tables C-1 and C-2 in Appendix C.

As described in the Methods section, we categorized duration of OC use in the included studies into four intervals: (1) 1 to 12 months, (2) 13 to 60 months, (3) 61 to 120 months, and (4) more than 120 months. These results, summarized in Table 20, show no time-dependent relationship as a function of duration of use. There was significant heterogeneity, with a t-value of 5.84 for 19 degrees of freedom, $p<0.0001$. However, the test was underpowered; there would have to be a 40-percent difference in risk of breast cancer by time period in order to detect significant differences.

Table 20. Estimated odds ratios by duration of OC use (breast cancer incidence)

Duration Interval	Odds Ratio (95% Confidence Interval)	P-Value
0–12 months	0.95 (0.83 to 1.09)	0.465
13–60 months	1.03 (0.92 to 1.15)	0.644
61–120 months	1.01 (0.90 to 1.13)	0.895
>120 months	1.04 (0.93 to 1.17)	0.457

Time Since Last OC Use

Eleven studies[183,185,188,191,195,196,203,206,208,210,216,218] were included in this meta-analysis examining the effect of time since last OC use on breast cancer incidence. Of these, 9 were case-control studies and 2 cohort studies. Five studies were rated good quality and seven fair quality. We did not include data in the meta-analysis for studies that only reported time since last use

data for a special population, did not have at least three categories for duration of use, or used a referent category other than never users.

As described in the Methods, we categorized time since last OC use into four intervals: (1) 0 to 5 years, (2) 5 to 10 years (3) 10 to 20 years, (4) more than 20 years. These results, summarized in Table 21, show a time-dependent relationship as a function of time since last OC use, with higher risk associated with more recent use of OCs and the odds ratio approaching 1 (no effect) by 20+ years of use. There was significant heterogeneity. The estimated value of σ is 0.12. The t-value is 4.95 for 11 degrees of freedom, p=0.0004.

Table 21. Estimated odds ratios by time since last OC use (breast cancer incidence)

Time Interval	Odds Ratio (95% Confidence Interval)	P-Value
0–5 years	1.21 (1.04 to 1.41)	0.0178
5–10 years	1.17 (0.98 to 1.38)	0.0776
10–20 years	1.13 (0.97 to 1.31)	0.1705
>20 years	1.02 (0.88 to 1.18)	0.7686

We also fitted a model to the individual reported odds ratios. The time (in years) was assumed to be the middle of the interval reported. The fitted model was odds ratio equals (1 + 0.2711 * EXP(-0.06551 * years) (Figure 25). The slope was significant, with a chi-square of 4.8 for 1 degree of freedom, p=0.0285. The model produced a slightly better fit than did the individual odds ratios in Table 21 and show a time-dependent relationship.